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## Address of Welcome\*

By S H BOYER, *President of the Minnesota State Medical Association,  
Duluth, Minn*

ORIGINALLY, physicians banded themselves together in order to keep their knowledge intact and their calling sacred, as witness the ancient guilds and the Oath of Hippocrates. So strong were these purposes that they have held through the centuries. Even today, though not always remembered, these purposes continue to be the chief motives that bind us together. Throughout antiquity, on through the dark ages and right down to the present time the medical profession has felt the influence of this tradition, and it has fettered us and made us feel almost as a thing apart from the social fabric in which we live and move and render service. So it is that in our changed world we have had difficulty in freeing ourselves from the bonds of habit, difficulty in extending and broadening our field of activities, difficulty in allying ourselves with and taking the lead in the various lay health activities of our time.

The increase in population, the congestion of the people in cities, the advent of the machine age and mass production, the changed economic conditions, the tremendous complexities of modern social and industrial life have resulted in all manner of

blocks and groups, whose chief aims are to study their relations to the body politic to the end that they may intelligently battle for their continued existence. The medical profession no less than other groups, and perhaps even more than others, must struggle to maintain its independence. The main body of our profession recognized this fact some time ago, therefore in their general organizations began to escape beyond the confines of tradition, to recognize conditions as they confront us, and prepare to meet them on a practical basis. To this end they added to their scientific organization what might be called a social science division. This is made up of many special committees, unheard of in the time of our fathers, whose work is to study all those phases of modern life with which we have been out of touch and to point out to us our relationship to those phases so that we may properly adjust ourselves to them, carry our share of the social load and maintain our identity as an individual, independent and progressive group.

This panoramic change in the social order based upon the rapid acquisition of new and vast knowledge, new machines and new methods, extends into the field of medicine, in which field new facts, new knowledge, new practices have increased by leaps and

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\*Delivered at the Minneapolis Meeting of the American College of Physicians, February 10, 1930



bands beyond anything of which we had ever dreamed. Small wonder then that men began to give special attention to one or another of the multitudinous subjects in the practice of medicine. There was presently to emerge from this intensive study the so-called specialist, more properly termed in most instances one with a limited field of practice. Indeed in most cases the specialist's knowledge outside of his chosen field gradually vanished from his memory, while the field itself steadily contracted until almost any really capable man outside the limited field could not fail to see that the one within knew and practiced only a few stunts or tricks. Happily however all were not like that. There were those who knew the need of a broad foundation of knowledge and aimed through their contacts to keep their foundations in repair the while they built special structures upon them. It was the men of this type who sought each other out and banded together into special societies "to keep their knowledge intact" and to add more to it, even as you who are here today have done.

With the passage of time many new specialties developed with their corresponding societies, all of them exclusive, all of them confining their activities to the scientific phase only of professional life. Whereas the official general societies prepared to exercise an active influence in the various social, economic, industrial and other movements having an important relation to the position of the medical profession in the body politic, the special societies appear to have moved

in the opposite direction. Two thoughts put out themselves in regard to all of these special organizations. One pertained to the effect they may have upon the parent body; the other to the desirability of holding aloof from the extra-scientific activities of the general societies.

That the organization of an additional society whose scientific purposes are identical with those of one or more existent societies would, on the face of it, appear to be a division of interest and of strength cannot be denied. Whether or not such is the fact will depend upon several factors. If all the officers of the new society yield an equal interest to the activities of both societies and spend an equal amount of time in the service of both, providing of course that the time and interest given are not less than before the new body was thought of, then the one has not weakened the other. But as it is only human to favor one's child it is reasonable to suppose that the above provisos will not obtain. In that case the result will be a division of strength and of interest with more or less injury to the original society. Should the new organization now fail to develop increasing strength in membership, attendance and production of scientific material there will be two weak societies instead of one strong one. Should the original body become so large as to become unwieldy, become so rich in accomplished members that comparatively few would ever have a chance to present worth-while papers, then it would be logical to suppose that the cause of scientific medicine would be

subverted by the birth of a new organization We trust the latter conditions rule in the present instance

We turn now, and with equal brevity, to the phase of extra-scientific activities Whereas the general societies, fully alive to the rapid and evolutionary changes transpiring in the social, economic and industrial world, have found it expedient to devote a considerable part of their thought and action to extra-scientific work, the special societies hold aloof from this field They seem to have deliberately, studiously aimed to avoid such duties It is almost as though the age old habit of exclusiveness, acting like an hereditary influence vice-like in its grasp, had caused them to revert to type This is probably as it should be, barring certain reservations, for if all of the special bodies should become active in this outside or extra-scientific work there would be no end to confusion and we would indeed be a profession divided against itself On the other hand if these special societies do not manifest an interest in such work they then very definitely reduce the influence of the national organization, because the public soon learns to know that a large part of our profession is organically indifferent to some of our most vital problems and comes to look upon us as a great body of presumably intelligent men, who are in reality so stupid that they neither know their common economic needs nor have sense enough to learn what these needs are and then to proceed with a solid front to secure them

Clearly then the special society, even though a source of scientific advantage to its members, becomes a source of weakness to the profession as a whole and will so continue unless the defect can be corrected in some way The problems of the profession are no longer wholly scientific and the special societies should recognize this fact Proper organization should establish points of contact with the parent society on the one hand and with all of the special societies on the other Providing these bodies endorse the parent body in its various activities the latter will speak with a voice of authority that will command respectful attention

The Minnesota State Medical Society is wise in organization and is known far and wide as being one of the strongest and best organized medical bodies in all the states Being so recognized its official welcoming spokesman has had the temerity to suggest to you a closer relationship between all medical bodies, a federation if you please, believing that this can be realized and greatly to the advantage of all concerned

Minnesota suggests that her splendid organic work serve as an example to be emulated, suggests and hopes that you strengthen your organization and grow strong and powerful in the cause of medicine

The members of the Minnesota State Medical Society welcome you to our fair state They know that mentally you will be gorged to bursting They trust the joys of the banquet

table will lighten the burdens of the days.

Again they welcome you and in the words of Jahweh as heard by the prophet Ezekiel, who envisioned himself as standing in a vast Babylonian plain "full of bones - - - and they were very dry,"—

"Lo, within you I shall put spirit,  
And ye shall live

I shall grant you sinews,

I shall raise up for you flesh  
I shall set over you skin.

Within you I shall put spirit,  
And ye shall live."

## Presidential Address American College of Physicians\*

J. H. MUSSER, M.D., *New Orleans, La*

EVERY year, as a result of custom and, by now, well established precedent, your retiring president appears before you and, in the annual address, presents to you the report of the activities of our organization, the American College of Physicians, during the interval that has elapsed between the yearly meetings, he is wont to comment on the events that take place during the yearly meeting, he very generally has suggestions to make for the betterment of the organization, and he comments upon the policies that guide it. This year the duty of addressing you falls on my shoulders. Perchance one is quite aware that when the word duty is used it implies very generally an act or deed that is a requirement or a task. But in the present instance this is far from the truth. To appear before this body as their elected head is an honor which no man can but feel is the culmination of his highest ambition. I am not unmindful that to address you is a privilege accorded to but few physicians. It is such a privilege that I cannot help but feel that, no matter how unworthy I am to have succeeded the distinguished men

who have preceded me, how incapable I may have been to take their place, to stand where they have stood, how inadequate my few talents may be to head such a splendid body of men as make up this College of ours, I repeat I cannot help but feel a glow of pride and a warmth of heart that surpasses any that I have ever before felt, to come before you tonight and to address a body whose membership is composed of the cream of the practicing physicians of this United States. Our Fellows come from every state in the country. In the aggregate they make up an organization whose members are active scientifically and professionally, whose purposes are of the highest and whose standards represent the best in medicine. The American College of Physicians is virile, progressive and always growing. It is a great organization and one to which any Fellow may feel a justifiable pride in belonging and whose officers appreciate fully the responsibility which goes with the honor of representing it.

Before proceeding with the accounting of the year's activities, let us pause to pay tribute to one who has meant so much to the College in the past and whose tragic death came to all of us as a heavy and cruel blow. John Phillips was taken from us in

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\*Delivered at the Minneapolis Meeting of the American College of Physicians, February 12, 1930

his prime. A keen scholar, an indefatigable and tireless worker, a beloved physician, a man whose counsel was sought and welcomed, his broad-minded, sane and serious judgment will be missed at the meetings of the Regents as his cheerful and sunny smile, the firm and friendly grasp of his hand, and his happy greeting will be no longer here to welcome us at this and at future meetings. In addition to this great loss the College has had erased from its rolls by the Great Bookkeeper the names of nineteen Fellows and three Associates. Some of these Fellows have been active in the organization, some have played a passive rôle, but all were fine men of the highest stamp professionally. It will be impossible to read even a brief obituary of all of these mourned Fellows, but I can not let the opportunity pass without saying a short word to the memory of three of these men whom I knew personally. One of them, Arthur S. Loevenhart, was a man of national reputation, a great scientist, a brilliant teacher, a clever investigator, his death removes from academic medicine one of its great leaders. John A. Witherspoon was a doctor of the old school, a practitioner of note and a consultant whose services were sought after throughout the South. His fame was not limited to but one section of the country, so well was he known throughout the United States that he was honored with election to the Presidency of the American Medical Association. C. E. de M. Sajous was one of the original members of the College. His reputation in the

field of endocrinology needs no reference here. His name was as well known in Europe as in this country.

It is but natural that in such a large body as the American College there should occur yearly a considerable change in the roster of the organization. Death has removed some, there have been several (four) resignations for various causes, no one of them in any way reflecting on the dignity of the College, nor the sincerity of its purposes. To replace these few who have gone there has been a large number of men selected for membership in the College. During the year 1929, there were elected from January 1 to April (Boston meeting) 100 Fellows and 53 Associates. To October 27, 82 Fellows were granted favorable recognition and at this meeting there will be recommended for full membership 88 names, and for associate-ship 49. During this same time there were an equal number of men refused admission to the organization because they could not meet the ever increasing qualifications that are required for membership and a very considerable number of applications were withdrawn even before they were brought to the Committee on Credentials. Despite the high standards required of prospective members, our numerical yearly increase is considerable. The thought arises as to just how large should the College be. Should we continue to expand and to grow at such a rate as we have in the past few years? It is true that with the new admission requirements, our growth will be presumably lessened for several years, but after this temporary regression

it is right to assume that there will be an ever increasing influx of proposals for membership. Mere size does not indicate any peculiar virtues, but a healthy growth is to be encouraged. How best to achieve this without becoming too bulky, and yet to keep our doors open to the type of man we wish to commingle with us means a delicate adjustment, a balancing which will require skillful handling by those who have the affairs of the College in their hands. Already the College has attained a size which prevents us from accepting many invitations to meet in the smaller cities. We require not only sufficient hotel space to accommodate a large group of men, but, also, because of the very important clinical features of the programs, our meetings must be held in medical centers where there are a sufficient number of hospitals to afford a diffuse, wide-spread selection of cases, and above all room enough to accommodate those who come to hear, see and learn at the clinics. I can foresee in the not far distant future that sectional meetings will be a part of our educational program in order to allow a getting together of all our members yearly.

One of the encouraging features of the past year has been the increased interest evinced in life membership by the Fellows generally. Some five of the Fellows, Ernest H. Falconer, J. A. Lepak, Francis M. Pottenger, William D. Sansum, and Austen Fox Riggs, have concretely shown that they appreciate the mutual advantages to themselves and the College of such a membership. To the College it

means much. These dues are set aside on a separate endowment fund which will be used to further the scientific aims of the College, for such purposes as the proposed establishment of a Memorial to the memory of John Phillips, an action which should and will redound to the credit of the College.

I have mentioned briefly, in discussing the size of the College, the difficulties that will be encountered in finding satisfactory meeting places. Let me dwell for a minute upon the tremendous demands that are made upon him who is chairman of the annual convocation of the College. Each year one of the Fellows volunteers to arrange the program. This requires not only the getting together of a scientific program, and the arrangement of clinics, but also a host of details must be attended to which require a tremendous amount of thought and time. I wish for a moment to congratulate Dr. S. Marx White, who has so ably gotten together this magnificent program we are privileged to enjoy this week. He has labored long and hard, and without thought of self.

One of the very real accomplishments of the College of Physicians is the publication of a superb medical journal, a journal which this year gave to its readers 1,370 pages of scientific material, medical abstracts, book reviews, editorials and College news. I sincerely hope that every Fellow of the College appreciates as he should the tremendous value of the sections devoted to abstracts and reviews. Written by a student of

medicine, they represent the mature thought of one who knows of what he writes and who from his wide knowledge can give a critical and unbiased opinion of his subject matter. We are fortunate indeed to have as the guiding hand of the Annals, one who works so devotedly and unselfishly, Dr. Aldred Scott Warthin

There is one other subject germane to this part of my address devoted to the present status of the College that I would make mention of in passing. Criticism has been leveled at us in the past for the relatively high fees demanded from the members of the College. Dr. Martin, in his Presidential Address last year, answered these unfavorable comments fully. Suffice it to say here that the Regents have ever before them this not entirely unjustifiable criticism. It will and has received their constant attention, but big things and great accomplishments require money and the College will do greater things in the future than it has in the past and will be of greater service to its members than it has ever been before. There are so many things it could and should do that a stultification of these possibilities by lack of funds, to me as an individual, seems unworthy of our splendid organization.

I would like to digress at this point and touch upon several subjects which are of interest to us primarily as physicians and which may not bear directly upon the business and interests of the College. It may be that such a digression is not inappropriate in view of what has just been said about affairs financial and will not be

out of place in addressing you this night. It is assuredly true that we are gathered here primarily for the purpose of learning, of hearing of the advances in medicine and of informing ourselves of what the other man is doing. Our meetings are purely scientific. May it not be that the College should interest itself in some of the problems of medicine that are agitating the public as a whole, as well as many forward thinking doctors, men of the profession who are not satisfied to live in the little world of routine practice, to limit their horizon to the care of the individual, but who see and appreciate that great changes are occurring in medical practice, and that even greater ones are bound to happen within this coming third decade of the twentieth century. The science of medicine has advanced with giant steps the last fifty years. We have been living in an age of great discoveries and tremendous advances, medical, physical, chemical and industrial. We have only just begun to assimilate many scientific truths within the last few years, and while doing this, have been prone to overlook facts of a practical nature that have to do with the profession as a whole. To the older medical man, satisfied with his limited sphere of activity, and thinking in terms of self, the changing educational, economic and social phases of medicine have meant but little. To the youngster just starting his medical life, things as they are seem to be things as they have always been, yet the practice of medicine when analyzed by the thoughtful thinker has altered tre-

mendously since the War Educational standards have been markedly raised, hospitals and hospital beds have increased at an eventful rate, industrial medicine has come forward with the increase in size of our great corporations by the amalgamations of smaller concerns unable to provide, from their limited budgets, for medical service for employees, state medicine in many guises is creeping in, public health activities are manifold and varied, the collection of medical specialists in co-operative groups is nation-wide. All these and many more factors, are revolutionizing perhaps not the science but at least the art of medicine and are changing the fundamental methods of practice of our fathers! Still greater changes are as sure to happen within the next twenty-five years as is the sun to rise to-morrow. The practitioner of to-day, I venture to say, would in 1955 be as a stranger in a strange land if lifted bodily from now to then, without the gradual transition that will take place.

The question arises as to the future of this great organization in relation to medicine, other than the scientific. Should we sit with apathetic indifference and watch the waves of popular caprice roll over us? Or should we endeavor to sound out and to find out the sentiments of the members of our organization in reference to many of the problems of present day methods in medicine. I grant you that it would be beyond the power of the College, and the pocket-book, to delve into such questions as the cost of medical care, the scarcity of phy-

sicians, state medicine and so on. Many of these problems can and should be left to organized medicine as represented by our country, state and national organizations. Here let me interpolate a word about organized medicine. I consider it the duty of every member of the College to belong to the American Medical Association. Only with such an organization will we be able to attain a solidarity which will prevent the individual medical man from being ridden over by nation, state, or lay and popular bodies.

To return to the subject of the future purposes of the College as to whether or not we shall as a body interest ourselves in vital contemporaneous problems. If the College of Physicians should go on record, after a survey of its members as opposed to or favoring such and such plans and schemes and ideas as crop up from time to time, would it not be of inestimable value to the profession as a whole or to investigative bodies to know that a group of doctors representing a cross-section of some of the best minds of the profession had taken a definite stand on the question? Let us analyze such a question as that of state medicine. Always has state medicine been a shibboleth of fear, a watchword of danger, to the average medical man. Yet what cogent reasons have we to fear the entrance of the state into medicine? Most certainly in Europe the physicians have greatly benefitted by increased socialism in medicine. The English panel system, fought courageously and bitterly for some years, has materially



improved not only the economic status of the physician, but aided him in the practice of scientific medicine. In our country it is said that one-third of all doctors receive more or less financial returns from governmental agencies. Consider the large number of men with whom you are personally acquainted who depend entirely or in part for their income from municipal, county, state or national bodies, be they school boards or the Departments of War, Navy or Commerce. Perhaps state medicine would do away with the large amount of gratuitous work that in urban communities a physician does in the out-patient departments of hospitals and in the inservices as well, while in rural sections of the country the poor man pays if he can and if he cannot, the physician treats him and his family just the same. Doctors are intensely individualistic. That is why when only superficial thought is given to the question of state medicine they oppose it and seem to be rigidly against it. Perchance were the Fellows of the College to give due weight to the pros and cons of the problem they might think differently. They would look at the question, not from a selfish point of view, but from an impartial angle. They would consider the other man as well as themselves. I do not know the answer, but I do realize that there is much to be said in favor of governmental medical aid to the poor, both from their standpoint and that of the physician. I believe that the Fellows of the College appreciate this as well and that a definite, unbiased expression of opinion could emanate from this source.

It may be that I have selected as an example a proposition at the moment unsuitable for exposition as being a thing of the distant future—which it is not. I will discuss briefly two others first, the so-called scarcity of physicians and, second, the cost of medical care. Before dwelling on either of these two present-day problems, let me call your attention to the fact that the greater part of the agitation now going on concerning them is provided by lay bodies. The individual physician is not questioned as to his opinion or to his idea of the solution of something that is decidedly in his realm.

As to the shortage of medical men. Does such a condition exist? Is it not a hypothetical condition which is causing uneasy discussion? Is it not that there is not a lack of doctors in certain regions, but rather a dissatisfaction because a doctor is not at the immediate beck and call of any one who may want him at the moment? It would seem to me that the American public has become used to having their every wish and want satisfied. Extremely few communities suffer from lack of medical attention, but because a doctor is not at hand for their immediate care they think they are neglected and suffering.

The College of Physicians represents doctors from every section of the country, from cities and towns all over the United States. A poll of the membership would show very definitely whether or not such a state as supposed exists, actually is present in any section of the country.

The ever increasing cost of sickness is another agitating question of the day. By inference it is always presumed that it is the high cost of medical attention that is responsible for this very real problem. Actually, this is not so. More money is spent for drugs than is paid doctors is one of the findings of an investigation in certain districts by the committee on the cost of medical care. Untold millions are spent for useless and worthless, even dangerous, patent medicines. Hospitals receive enormous sums each year, partially because patients want the best accommodations in these institutions, whereas were they to go to a hotel they would not select the most expensive suite in the highest priced caravansary in the city they are visiting, but would choose a room within their means in a cheaper hotel. The cost of unnecessary nursing must be added to the bill, as well as many other expenses, too numerous to enumerate. The physician finds that while he presumably is responsible for this high cost of getting sick, actually with the characteristic altruism for which he is always noted, it is he who is willing that his bill be the last paid, and he is the only one who is expected to reduce his charges. The economic disruption of the individual and the family is a real problem and a live one, but I do protest against the very general conception that the doctor is the responsible agent. A frank and free discussion of the subject at one of the yearly meetings might be a real assistance to those who are attempting to find the correct answer as to how the middle class man with small income

can finance illness. While it is unlikely that some brilliant scheme might be presented to the world at our annual convocation which would materially aid in the solution of the enigma, at least an expression of opinion could be had from a body well qualified to make such a stand.

It may be that there has been found among the Fellows a marked divergence of opinion concerning the possibility of increasing the activities of the organization and more particularly of removing our self-imposed limitations of dealing only with scientific medicine and to discuss at future meetings certain economic, social and financial phases of medical practice which would interest a considerable number of our membership. It can be readily appreciated that such a step is well outside of present policy, which has confined itself entirely to the presentation of scientific papers, the publication of a splendid medical journal and a very limited social program. I would not propose that there be any very great upheaval in our present arrangements. The College is primarily and entirely a body devoted to the scientific aspects of internal medicine. As such it has a very definite place in medicine, acting more or less as a certifying body which puts the stamp of approval upon its membership as men qualified to handle adequately and thoroughly by the best available methods patients ill with diseases of certain types. Should we extend our field of vision and enter into wider fields, discussing and possibly deciding upon matters which are decidedly controversial? Such a change

in our proceedings would make for a decided change in the policy that now governs the organization. My personal view is that this should be done in a limited way. The three major functions of the organization I have outlined, but certainly there are other minor obligations to our members and to the profession at large which we should undertake.

In conjunction with the important questions that I briefly sketched in the early part of my address, it might be entirely possible each year to deal with one or two of these subjects or such other problems that might at the time be thought-provocative and fact-inspiring. Specifically, one session of our program might be devoted to the cost of medical care. This session could be more or less informal in the form of a round table discussion, the proceedings to be opened by several papers which were authoritative as a result of collection of facts, data and statistics. Succeeding this there could be a general discussion in which various Fellows could express their views and opinions. The preliminary paper or papers would take from 20 to 30 minutes in being presented, while during the general discussion the speakers should be limited to five minutes. If there was any uniformity of opinion, resolutions might be passed expressing views one way or the other. It would seem advisable to determine upon a subject for discussion some twelve months ahead of the succeeding meeting and either a committee or one man be appointed for the purpose of getting together facts and collecting data largely from the individual mem-

bers of the organization. Such information could be collected by the questionnaire method and they could be analyzed and then submitted to the body as a whole in the form of one of the preliminary papers just mentioned. The five minute discussions would be largely to permit any individual Fellow to dilate upon and to enlarge upon his opinions which were answered briefly in the questionnaire. By methods such as this our organization would definitely go on record as to the feeling of the majority of its membership upon such questions. It would give to the bulk of our membership the opportunity of expressing themselves. Many of our Fellows coming from smaller communities and not connected with large hospitals and clinics, feel that their experience is too limited to prepare papers to be read at the annual session. While this is very largely, I believe, an entirely too modest assumption, nevertheless it is so, but any physician or internist, no matter where located, has the opportunity of cogitating upon and thinking about and coming into contact with some of the contemporaneous problems of medical practice. They may be loath to express themselves concerning scientific subjects, but certainly many would freely and willingly undertake to delineate on these questions of the day.

And now I would like to say a word to the new members who have just joined the American College of Physicians. I would say to you that you are welcomed to our organization. You are in a position to give much and you are fortunate that you will

receive much from your associations with the other internists in our large group. You can give much by attendance at the meetings. Your mere presence will add to the enthusiasm of any given meeting, for the presence of a goodly number of auditors is an inspiration to any speaker, and you can help, aid and assist in this particular way. You are in a position to contribute to our scientific programs. You can give by contributing to the Annals of Clinical Medicine. You receive in turn membership in an organization which is composed entirely of representative, high-class, successful practitioners of medicine. Your qualifications as doctors, your integrity of purpose and your high ethical standards have been judged not only by the Committee on Creden-

tials, but also by those physicians who are in your city and locality, and you, in turn, will have the privilege of passing upon future candidates from your section of the country. By your work, by the approval of your fellow practitioners, you have been shown to be men of industry, capable, well educated and governed by the high ethical principles of the medical profession. Membership in our organization gives to you a professional stamp and attributes an ethical standard by which we should all be trying to live and to practice. I feel that you are to be congratulated upon your election to the organization and by the same token I believe that the College is to be congratulated upon having you as members. In your hands lies the future of the College.

# Colloids in Medicine\*

By ROSS AIKEN GORTNER, *Professor of Biochemistry in the University of Minnesota, St. Paul, Minn*

**C**OLLOID chemistry has been defined as "the chemistry of the infinitely little." It can perhaps be better defined as *the chemistry of films, surfaces, and interfaces*, for the peculiar energies which are available for the reactions of colloid chemistry are those energies which are characteristic of surfaces and interfaces

For purposes of classification it has been rather generally agreed that particles which range from 10 m $\mu$  to 0.5 m $\mu$  lie within the colloid realm, and the reactions which such systems show can in the last analysis be traced to reactions which are induced by a decrease in the free energy which resides in the interfaces present in the systems. It is for this reason that the chemical nature of the finely divided colloidal material is in many instances relatively unimportant and that colloidal sols prepared from very different types of chemical materials may exhibit very similar properties or induce similar reactions.

The surface area which characterizes colloidal systems is almost beyond comprehension. Thus, for example, if a cube of material one centimeter on

an edge with a total area of six square centimeters is subdivided into material 0.1  $\mu$  on an edge, the surface area has been increased to 2,117 square feet, and if one progressively decreases the size of the particles to the lower limit (10 m $\mu$ ), one arrives at a system which contains 1,000,000,000,000,000,000 particles, having a total surface area of 211,740 square feet. In such systems there is an alteration of the affinities and energies of the molecules and atoms in the surfaces, so that they become different from those in the bulk of the material, and it is to these altered affinities that colloid systems owe their peculiar reactions

All permanent colloid systems are stabilized either by the presence of an electric charge (a so-called Helmholtz double layer) which exists at the surface of the micelle or because of the affinity of the particle for the solvent in which the particle is dispersed, and in general those colloid systems which are characteristic of living organisms possess both factors of stability. Those colloids which show no appreciable affinity for the medium in which they are dispersed are known as lyophobic colloids, whereas those which combine with the medium are termed lyophilic colloids.

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In a discussion of colloids in medicine one could perhaps devote considerable attention to the rôle of lyophobic colloids in the diagnosis of disease, or of the colloidal metals, such as lead or copper, in the control of malignant growths. Thus, for example, the precipitation limits of systems containing colloidal gold and (later) gum benzoin<sup>1,2,3</sup> have been utilized to differentiate paretic from normal cerebrospinal fluid. While such colloid chemical studies are of undoubted importance to medicine, there are certain other problems, pertaining to all living organisms, which deserve the attention of the physician and the research worker.

The human body—in common with all living organisms—is composed of chemical materials which, by and large, may be classified into five great groups, (1) proteins, (2) carbohydrates, (3) fats and lipides, (4) inorganic salts, and (5) water. There is, it is true, a number of compounds, which are characteristic of the cells or tissues, which do not fall definitely into any one of the groups of the above classification, but the amount of such compounds is extremely small, although undoubtedly in many instances they play very important rôles in physiology. Since, however, we have little or no knowledge as to the rôle which such compounds may play in the living organism, considered as a colloid system, they can be omitted from the present discussion.

Of the five great groups which we have noted, the proteins are certainly in the colloidal state. They belong to the group which has been classified as the lyophilic colloids. In the biologi-

cal organism they exist associated with relatively large amounts of water, and in most instances are stabilized as a colloid system both by their hydration and by the presence of an electric charge.

In the plant organisms the carbohydrates may comprise a very considerable part of the tissue, and such complex carbohydrates as cellulose, starch, pentosans, gums, and pectins may account, even to a major degree, for the colloidal behavior of plant tissues or organs. In the animal kingdom, however, carbohydrates or carbohydrate derivatives appear to play an almost negligible rôle, although, when we know more of the colloid chemistry of nervous tissue, it may well be that the carbohydrate radicals which are present in the cerebroside may be found to contribute materially to the physico-chemical properties which are peculiarly characteristic of nervous tissue.

The fats and lipides exist in the living organism largely in the form of emulsions, and since emulsions are systems which are characterized by a dispersion of oil-in-water (or water-in-oil) and accordingly possess large internal surface areas, emulsions may be properly classified as falling within the subject matter of a discussion of colloids. Certain of the lipides, notably lecithin and the associated phospholipides, show marked affinities for water and may be classified as true lyophilic colloids.

The salts and molecularly dispersed solutes characteristic of cells are in general considered as existing in true solution in the water of the cell or tissue, and, as such, as obeying the

classical laws of physical chemistry. However, the presence in such solutions of extremely great surface areas, such as characterize the colloiddally dispersed proteins, fats, etc., brings about conditions whereby a very considerable proportion of the supposedly molecularly dispersed materials may be adsorbed at the interfaces and thereby be removed from the aqueous phase. The chemical reactivity of molecules or ions when present in an adsorbed condition is vastly different from the chemical reactivity of such molecules or ions in a true solution, which possibly accounts for many of the peculiar reactions of living matter that cannot be explained by the application of classical laws.

The human body contains more than sixty-five per cent of water, and in certain living organisms, such as the *Medusae*, the percentage of water may be as great as ninety-nine per cent. The fact that a part or all of this water may exist in a different state in the living organism from that which characterizes water in bulk has been rather generally ignored in our studies of biochemistry and physiology. Undoubtedly the water which is associated with the lyophilic colloids possesses properties very different from those of water in bulk, and in any consideration of physiological problems, one is not justified in dissociating the protein, which is present, from a very considerable proportion of the water in which it is dispersed. The protein micelles are hydrated, and the unit which is reactive is not only the amino-acid complex, which we call protein, but is the entire hydrated micelle. The reactions of the cell will never be ex-

plained by studies of the dry chemical constituents which comprise that cell, and if the cell reactions are ever explained, they will be ascribed to reactions which are characteristic of a colloidal system in which water is the chief constituent. Undoubtedly there exists within the biological organism and within each cell and tissue of that biological organism an equilibrium between "free" and "bound" water, *i.e.*, between that portion of the water which is free to act as a solvent and that portion which is intimately associated and "bound" upon or "dissolved" in the organic micelle.

Apparently the first suggestion that a free  $\rightleftharpoons$  bound water equilibrium exists in the body was proposed by Balcar, Sansum, and Woodyatt<sup>4</sup> under a subtitle, "A Physicochemical Theory of Fever." In this paper they proposed a theory that fever resulted as an alteration in the free  $\rightleftharpoons$  bound water equilibrium which characterizes normal tissue and that it was the disturbance of this equilibrium which brought about the temperature response. They were unable, however, to devise methods for demonstrating a changed equilibrium.

That "bound" water, as such, is a factor in physiology was demonstrated in 1922 by Newton<sup>5</sup> in a study of the nature of winter-hardiness in plants, using a method proposed by Newton and Gortner<sup>6</sup> for the approximate estimation of "bound" water. In later studies, Newton<sup>7,8</sup> confirmed and extended his original observations and showed that not only winter-hardiness but also drought resistance<sup>9</sup> was influenced by a free  $\rightleftharpoons$  bound water equilibrium. Somewhat later, Thoenes<sup>10</sup>

devised a new technic for the study of this problem and demonstrated that the muscular tissues of young animals possessed a greater proportion of "bound" water than did the muscular tissues of older animals. This is in the direction that one would expect. We know that colloid gels, such as gelatin, silicic acid, agar, etc., prepared under laboratory conditions undergo an aging process which is characterized by a syneresis of the liquid from the gel and a lessened water-holding capacity of the gel. To what extent the decreased water-holding capacity of biological tissues may be correlated with problems of senescence, *arteriosclerosis*, and decreased glandular functioning cannot be decided from our present knowledge and must await future biocolloid research. Reasoning from analogy, however, this field promises exceedingly important developments.

Following the technic of Thoenes, Robinson<sup>11,12,13,14</sup> studied the problem of winter-hardiness and related phenomena in insects and demonstrated that winter-hardiness in insects differed in no essential particular from winter-hardiness in plants, in that both phenomena are characterized by a binding of the water by the lyophilic colloids present in that organism.

We have, therefore, from these studies apparently a generalization of a free  $\rightleftharpoons$  bound water equilibrium which is shifting within the organism in response to external stimuli, and data are already available which indicate that internal stimuli are capable of producing as great or greater changes in this equilibrium. That such changes are of importance in medicine

must be obvious. The whole problem of edema rests in the last analysis on the affinities of the lyophilic colloids of the tissues for water. A decrease in the water-binding capacity of the tissues will release fluid into the tissues or body cavities, whereas an increased affinity will draw water from the blood or lymph stream, and thus alter the equilibrium which characterizes health.

Robinson<sup>15</sup> has continued his studies on the water equilibrium at the Otho S. A. Sprague Memorial Institute and has demonstrated that from the colloid chemical standpoint the living organism must be looked upon as an entity and that alterations in the free  $\rightleftharpoons$  bound water equilibrium in the blood stream are reflected by alteration in the muscular tissue. His studies indicate that many of the anesthetics and drugs produce a very definite alteration in the free  $\rightleftharpoons$  bound water equilibrium of the organism. If Robinson's work is borne out by future research, it will necessitate the writing of a new physiology, the physiology of the organism as a whole rather than the physiology of individual cells and tissues.

Inasmuch as proteins comprise the major group of organic compounds present in living tissues, certain of the colloid problems of protein chemistry become of unusual significance. In 1908, the American Society of Biological Chemists and the American Physiological Society appointed a joint committee to prepare a logical classification of the proteins. In the report of this committee<sup>16</sup> the words, "solubility" and "soluble," occur many times and in many instances "solubility" is



the criterion upon which protein classification is based. Colloid researches, however, have demonstrated conclusively that with the probable exception of the albumins,<sup>17</sup> proteins probably do not exist in water as molecular dispersions but rather as colloid micelles, in which case the water "solubility" is meaningless and the colloid term, peptization, should be substituted. Globulins were defined as "simple proteins, heat-coagulable, insoluble in water, but soluble in dilute solutions of the salts of strong acids and bases," and for twenty years this definition was unchallenged. In 1928, however, Gortner, Hoffman, and Sinclair<sup>18</sup> undertook the isolation of a series of proteins from wheat flour. Using in their study twenty-two different salt solutions, most of them in four different concentrations, they found that each salt solution in each concentration extracted a different amount of protein from the wheat flour. Thus, for example, using equi-ionic (1.0 N) concentrations of the potassium halide salts and taking care to adjust the solutions so that they had identical hydrogen ion concentrations, they found that potassium fluoride extracted 13.07 per cent, potassium chloride 22.77 per cent, potassium bromide 37.22 per cent, and potassium iodide 63.89 per cent of the total nitrogen. The "solutions" of protein in these salt solutions were optically clear. These authors, therefore, definitely raised the question as to *what salts* in *what concentrations* should be utilized for the extraction of a protein entity which could be characterized as a "globulin," and expressed the viewpoint that none of the salts in any of

the concentrations used would extract a definite single chemical entity.

In a continuation of these studies, Staker<sup>19</sup> investigated a large series of seeds and grains, including most of those which had been earlier investigated by Osborne. Staker's findings were in every respect a confirmation of the earlier studies of Gortner, Hoffman, and Sinclair, as indicating that protein solubility was in reality the peptization of lyophilic colloid micelles.

Following a rigidly prescribed technique of protein extraction and purification, a given amount of a given product can always be isolated from the same biological starting material, but if the technique of isolation or purification is altered in any way, then the end product will be obtained in different amounts and will show different physical and chemical properties. We must therefore recognize the fact that when we study the proteins we are dealing with colloid systems and that these colloid systems do not obey the laws of classical chemistry. This fact becomes of especial importance in problems of immunology. The globulins have been divided by "solubility" methods into euglobulins and pseudoglobulins, and there is an ever increasing tendency toward further subdivision. It may be that such fractionation will result in scientific advances, but there is no assurance that either euglobulins or pseudoglobulins represent definite chemical entities or that any of the proteins which have been isolated from biological tissues represent an entity which was actually present in the living organism. This viewpoint has been very admirably expressed by Abderhalden<sup>20</sup> when he

states, "Each conception in regard to particular structural relations in proteins, and especially of those which are concerned in living processes, must take into consideration all their reactions, their ready transformation from the natural to the denatured condition, and their greater or less lability. It is certain that proteins in protoplasm have properties of which we are at present entirely unaware. We study proteins almost invariably in a greater or less changed condition. On the one hand, we have proteins which in a certain sense are denatured in the organism, and outside of the organism undergo further changes. Thus, for example, we see the silk threads, the web of the spider, the byssus of certain mussels, etc., which are extruded as a liquid, changing to an inert solid. From a very labile form they are transformed into a very stable structure. In living processes we deal with the very reactive cell proteins which regulate in a fine degree the reactions of the cell, but when death

ensues, the cell proteins coagulate and lose in a large measure their characteristic physical behavior."

These conclusions of Abderhalden cannot be too strongly emphasized. We will never explain the colloid reactions of a cell by the colloid reactions of any one of the components of that cell; neither will we explain the colloid reactions of an organism through a study of the colloid reactions of individual cells or tissues of that organism. Colloid chemistry, as applied to biology, is still in the exploratory stage. Much of new technic has been introduced in the past few years and much more technic must be devised before we can hope to solve many of the major problems of physiology. Since, however, the chief constituents of living matter are in the colloid state, the technic and viewpoint of the colloid chemist offer the physiologist and the physician one of the most valuable tools in the study of vital phenomena.

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# Cerebral Localization\* \*\*

LEWIS J POLLOCK, M D , *Chicago, Illinois*

THE importance of the grey matter of the cerebrum was first emphasized by Gall and Spurzheim. The cerebral hemispheres were thought to be divided into as many pairs of particular organs as the functions they subserve.

In 1825 G R Boullaud described the symptoms of aphasia in a series of cases and was able to show that the frontal lobe was diseased in all cases. A little later (1836) M Dax demonstrated that cases showing disorders of spoken language suffered from lesions of the left cerebral hemisphere. In 1861 Paul Broca confirmed the conjecture that there was a given center for sensation, motion, and special memory in the left cerebral hemisphere, specifically, in the lower segment of the third frontal convolution.

A brilliant introduction of a new chapter in our knowledge of the function of the brain was effected by the work of Fritsch and Hitzig (1870) in their memoir "On the Electrical Excitability of the Brain." They gave the name of centers to those areas which when excited by direct appli-

cation of a galvanic stimulus reacted by muscular movement.

Ferrier's (1873) use of faradization of the cortex enabled him to precisely chart out a number of centers in the cortex of the dog. H Krause, Beevor and Horsley described the excitable zones of the cerebral cortex of the monkey, and later observations were made on man by Ferrier, Horsley, Beevor, Bechterew and F Krause. The theory of cerebral localization having been established, further physiological research, clinical observation and correlation with pathologic studies and biopsical observations permitted by neurosurgery, rapidly led to a comprehensive knowledge of the localization of motor areas, sensory areas, and areas of hearing, speech, taste and vision. The function of the basal ganglia, the cerebellum, the brain stem—in short of the whole central nervous system has in a remarkably short time been put to experimental proof, and although much remains to be learned the chief functions of the central nervous system are known.

Because of this knowledge the localization of well developed lesions in the central nervous system may readily be accomplished in the majority of cases. Such localization is of value not only in relation to the removal of tumors, or drainage of abscesses, but also in

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\*From the Department of Nervous and Mental Diseases, Northwestern University Medical School.

\*\*Read at the Meeting of the American College of Physicians, Minneapolis, Minn., February 10, 1930.

the matter of diagnosis, as in the differentiation of subarachnoid hemorrhage resulting, for example, from a ruptured aneurysm from intracerebral hemorrhage, of a cerebral abscess from an extradural one, or meningitis or sinus thrombosis.

It is of value in recognizing certain disease entities, as progressive lenticular degeneration, parkinsonism, and other diseases of the basal ganglia, in determining the particular vessel involved in a thrombotic process, as in lesions of the posterior-inferior cerebellar artery, and in cases too numerous to mention

When of sufficient size and of certain character the localization of most of the tumors may be accomplished. It is necessary only to allude to the principal signs and symptoms occurring as the result of lesions of a few of the parts of the cerebrum to illustrate this. Bitemporal hemianopsia is found chiefly in lesions above the chiasm, in pituitary adenomas; prefrontal tumors are characterized by weakness of the facial muscles chiefly in the movements evoked during emotion, by convulsions and mental change. When on the left side there is often disturbance of speech. Lesions in the pre-central gyrus are characterized by focal or jacksonian convulsions in addition to motor paralysis. This motor aura of a convulsion is analogous to such sensory ones as are seen in lesions of the uncinate gyrus, wherein a sensation of a disagreeable odor precedes the convulsion, and in a lesion of the occipital lobe of visual hallucinations preceding a convulsion. Temporal lobe lesions frequently are

associated with quadrant defects in the field of vision and occipital ones with hemianopsia. A combination of a hemiplegia with a hemianesthesia and hemianopsia is indicative of a deep-seated lesion about the internal capsule. The relative convergence of function of sensation, general and special, permits the utilization of localizing lesions of the angular gyrus by alexia, of cortical involvement of the visual centers by the presence of central blindness, or of disorientation as to place; for example, when a patient with a homonymous hemianopsia loses himself in his own home

Were it true that all tumors resulted in so positive objective phenomena so readily discerned, it would be unnecessary to read further. If one's memory failed, a consultation of any book on neurology would enable one to easily fit the signs and symptoms into any particular localization. Unfortunately, this is not the case. The purpose of this communication is to point out some particular, and, possibly to many of you, trite methods of observation of some signs which are of assistance in the localization of cerebral lesions.

Let us suppose that one is called to see a case of a patient in coma, who has a history of headache and vomiting, who has a choked disc, and has had a sufficiently profound mental change to justify the diagnosis of a frontal lobe tumor. Which side is involved? Or, given a man with typical uncinate gyrus fits, indicating a lesion of the temporal lobe, but who has no defect in the field of vision, which temporal lobe is involved? Or, a man giving a history of epileptic convul-

sions preceded by hallucinations of red flames, how are we to determine the presence of a hemianopsia if he is semistuporous or has moderate clouding of consciousness?

One of the most fruitful sources of information is the condition of the reflexes. Of course, as you recall, in all cerebral lesions affecting the pyramidal tract, the deep reflexes are increased, the superficial ones diminished or absent, and at times such pathological reflexes as the Babinski are present.

Not only is it necessary to determine the presence or absence of these reflexes, but it is necessary that changes in their response to stimuli fit together in a logical sense. If one obtains what he considers to be a Babinski and the deep reflexes of that side are not increased, and the cremasteric and abdominal reflexes are brisk, considerable doubt is thrown upon the validity of that observation.

This does not mean that all of the deep reflexes must be increased on that side, or that all of the superficial ones must be absent, but if any difference in the response of the deep reflexes occurs they must predominate on the side where the Babinski is elicited, and when the superficial ones are diminished it is on that side that the diminution must be present to enable one to use the Babinski sign as a localizing reflex. If one finds an apparent weakness of the right side, if the superficial reflexes are more brisk on that side and the deep reflexes diminished on the same side it is likely that what appears to be weakness is defective movement due to a lesion of the cere-

bellum or its connections. Rarely may we find an increase of deep reflexes on the same side as a cerebellar lesion resulting from pressure of the *opposite* crura cerebri against the incisura. So important is this difference in reflexes that one should never be content with simply striking the patellar or Achilles tendon carelessly with a hammer or, worse, with the hand. Not only must one carefully record the rapidity and extent of movement of an extremity to stimuli of increasing amounts, carefully comparing the two sides, but also that degree of stimulation necessary to first evoke a deep reflex must be ascertained, and *all* of the deep reflexes must be examined. When no difference may appear to be present in the knee-jerks, epipatellar blows may enable one to determine such a difference. When the Achilles-jerks may seem equal when the patient is examined in bed, a difference may be made out when the patient kneels on a chair and the tendon Achilles is tapped with succeeding different degrees of force. Similar care is necessary in examining the superficial reflexes. The presence or absence of a Babinski or the absence of a plantar reflex is not all that can be elicited from stimulation of the sole. The character of withdrawal, the difference in degree of stimulation necessary to provoke any motor response, are equally important. It is not sufficient to stroke the inner surface of the thigh with a pin to elicit the cremasteric reflexes, or the abdominal wall to elicit abdominal reflexes. The strength of stimulation must be carefully determined, and although stroking the abdominal wall

with a pin may evoke a reflex, if one lightly rests a pencil upon the lateral portion of the wall and stroke inward, using only the weight of the pencil, the reflex may be obtained on one side and perhaps not on the other. Often when these little differences in reflexes are fitted together, such as an increase of all deep reflexes and a diminution of all superficial ones on one side, they may suffice with little else to localize the side of the lesion. More frequently motor disturbances are needed to further justify a diagnosis. When gross weakness occurs of course it is a simple matter, but very often there is little difference in the grasp of the patient. He is able to perform all movements apparently with good strength. He may be able to walk well and be unable to state definitely as to the existence of any motor disability. It is to this particular part of the examination that I wish to direct your attention.

Many little signs of hemiplegia have been described, but I will allude chiefly to those which have been found useful. At times it is necessary to determine the paralyzed or weak side in a semi-stuporous patient or a comatose one. Although it has been stated that under such a condition the paretic upper extremity falls more slowly when released from a passively extended position I have not found it so. With the patient lying on the back when the arm and forearm are extended to a right angle with the trunk, with the arm supported and the forearm released on the paralyzed or weak side it falls readily and completely, and if

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forearm strikes the face it still falls promptly, at times striking the face. Rarely it is imperfectly deflected. When the whole extremity is allowed to fall it falls flail-like. In contrast, the other side falls slowly, usually never strikes the face but is checked. Often it remains extended for a time. The paretic cheek often puffs out with expiration. When one attempts to separate the lids, the resistance on the normal side is greater, and on the paretic side the eyeball often rolls upward when the attempt to resist the pressure is ineffectual. The lower extremity at times is slightly rotated outward. When elevated and dropped it falls rapidly to the bed. When passively flexed, with the heel scraping against the bed and suddenly released, it is rotated outwardly and slides down to an extended position. While being flexed the smooth tension felt on the normal side is lacking. The umbilicus may be drawn slightly to the side opposite the weakness, and if inspirations are sufficiently deep to at times produce an upward movement of the scrotum, the movement is less on the affected side. Although both upper and lower extremities may react, by flexor withdrawal to stimulation with a deep pin prick, the character of the movement often differs in degree or efficiency. Particularly can this be made out by pricking the abdominal or thoracic wall wherein the unaffected upper extremity is the one which reaches out for the painful area. Of course, the conjunctival reflex on the affected side is lessened. When the face or forehead is pricked frequently asymmetry of facial move-

ments may be seen, even when the extremities react equally well. The nasolabial fold is deeper on the normal side, the lids are closed more strongly, the angle of the mouth drawn further to the side, and if drooling is present it occurs at the angle of the paretic side of the lips. In inspiration the aperture of the nares on the unaffected side becomes wider.

Here one may refer to the examination of ocular movements in coma. When the head is rotated to one side the eyeballs rotate to the opposite side, and extraocular muscle palsies and paralysis of conjoined movement of the eyeballs are thus discovered. Often one may even ascertain the existence of a hemianopsia by striking at a patient from one and then the other side and on the blind side of the visual field fail to produce winking. Similarly, approaching the blind side of the visual field with a lighted match may fail to evoke winking, whereas winking occurs on the normal side.

When the patient is conscious many other little signs may be observed when gross methods of examination fail to reveal any motor disturbance. As one observes a patient lying on his back, the palpebral fissure on the affected side is wider, at times spontaneous winking is not as frequent and is incomplete on this side. The conjunctival reflex may not be as effectual or easily elicited. Passive movement of the upper lid on the affected side is accompanied by less resistance, if carefully observed. The aperture of the nares is smaller. The nasolabial fold is not as deep. Rarely slight moisture may be made out at the angle

of the paretic side of the lips. Although the tongue may be protruded in the midline the distance from its edge to the angle of the mouth is greater on the normal side. When the patient shows his teeth the affected side may lag slightly, or the nasolabial fold not increase in depth. Strong effort to bare the teeth on the unaffected side is accompanied by contraction of the platysma, on the affected side this very often is absent. Attempts to close the lids forcibly will show greater wrinkling about the lids of the unaffected side.

It is of great importance to observe the patient's face in repose, in voluntary action and in motion in response to emotion. Voluntary motion may be perfect but slight asymmetry exist at rest, and very often only the unaffected side will move in talking and particularly crying and laughing. Rarely the opposite state may be found.

In general, even in the absence of demonstrable weakness of the upper extremity, some clumsiness, defect in associated movements, greater fatigability, and at times tremor will be found on the affected side. With the patient lying on his back with both his upper extremities outstretched before him the affected extremity will fall downward slightly, or deviate outward or inward after a short time. When repeatedly abducting and adducting the fingers and thumb upon command, the unaffected extremity is held rigidly extended, the affected one is abducted and adducted with each movement of the fingers. Whereas all of the fingers of the unaffected hand are abducted and adducted, on the affected hand



only one or two are so moved. The fingers often are deflected to the ulnar side and flexed at various angles at the metacarpo-phalangeal joints. At times the movements are tremulous, often the response to the command is confused. When making a fist and opening the hand repeatedly upon command the affected hand is closed to differing degrees. Upon the unaffected side the hand is extended at the wrist when the fingers are completely flexed; not so on the affected side. Throughout both of these examinations the affected extremity continues to fatigue and gradually sink downward. Associated movements of the arm at the shoulder of elevation and sinking are seen on the affected side. The patient is observed to look at the affected hand while performing the tests, because he is in a way conscious of the greater effort necessary to perform these movements. Babinski has described a test which has been found of some value. The affected side, when the extremities are placed vertically with the palms facing each other and the hands loosely shaken, pronates.

With the upper extremities extended forward, the index fingers pointing to the foot of the bed, the index finger of the affected side deviates downward and to the ulnar side. The hand at times deviates to the ulnar side. When asked to lift the extremity up and bring it down to the examiner's finger, the affected extremity, although no past pointing is present, will not move as smoothly. The extent of movement upward and downward will vary, the forefinger will be brought down on the examiner's finger with varying de-

grees of strength, usually bearing down hard, whereas on the normal side the finger will be brought to rest on the examiner's finger with precision and accuracy. When the unaffected extremity is raised the affected one is slightly lowered, and when the unaffected one is lowered the affected one is raised. While performing repeated lifting and lowering of the unaffected extremity the outstretched affected one begins to sink slowly. Gradually it may sink almost to the bed without the patient's apperception.

Rapid drumming of the index and middle fingers of the affected side is difficult and clumsy, although adiadochokinesia is not present, repeated apposition of the palm and dorsum of the hand to the thigh is clumsy and slow on the affected side. Touching the finger to the nose or finger to finger may elicit slight clumsiness, uncertainty or tremor. The general character of the handwriting may be changed if the right side is the affected one.

In the lower extremities repeated passive rapid flexion and extension of the unaffected side is characterized by smoothness of movement, resisted by slight tension, at the height of flexion the flexed thigh and leg come to rest with the foot upon the bed, smoothly, without any lateral movements, and when passively extended the movement is timed so that no sudden jerk occurs. On the affected side less tension is felt, the movement is less smooth, at the height of flexion when the extremity is released, there is adduction, abduction, or both, to a slight degree, when passively extended often

no tension is felt and the leg is allowed to suddenly fall out in extension with slight outward rotation. When the extremity is repeatedly flexed and suddenly released so that the sole falls upon the bed the affected extremity sways and then extends to a shorter or longer distance. When now a sudden pressure of short duration is applied to the back of the leg it extends suddenly or sways. On the normal side the foot falls firmly to the bed, with the thigh and leg in upright position and when pushed it extends a distance proportionate to the push. The passively elevated and slowly released unaffected lower extremity is held in that position for a considerable time. The affected side fatigues, sways and is tremulous. Passive dorsal flexion of the normal foot is accompanied by active contraction of the tibialis. This at times does not occur at all on the affected side but usually is less marked. Babinski's combined trunk-thigh sign is often valuable. The patient lies upon his back, the feet separated about a foot, and the forearms flexed across his chest. Attempts to assume a sitting position are associated with elevation of the affected lower extremity. Attempts to adduct the unaffected extended lower extremity are associated with adduction of the affected one. Strumpell's tibialis sign is at times valuable although it often appears only after other evidence of involvement of the pyramidal tract is present. When the patient flexes the affected extremity with the foot above the bed the foot is held dorsally flexed to a right angle on the affected side. In placing the heel of

the affected side upon the opposite knee the movement may be uncertain and discontinuous. While the heel is resting on the knee slight swaying may be seen as well as abduction. If now one pushes the flexed extremity outward either disproportionate swaying occurs or there is a tendency for the heel to slip off the knee.

While walking a slight lagging of the affected side may be noted. At times the associated swinging of the affected upper extremity is diminished. Hopping on the affected side may be normally performed when once started, but very often the patient is unable to start hopping on this side until many attempts have been made.

The demonstration of motor disability of one side when accompanied by the reflex changes destined to be present when that pyramidal tract is involved definitely localizes the side of the lesion and serves to localize such lesions in the prefrontal and temporal lobes without visual field defects. It is necessary in certain cases to differentiate slight evidences of cerebellar dysfunction from those of motor disability. Commonly the defects in synergy in the latter are fairly easy to determine, and involvement of adjacent parts—as the occurrence of a sixth nerve palsy on that side—are sufficient to call attention to the cerebellum even if the auditory nerve is unaffected and labyrinthine function normal. Often the Babinski-Weil test is of assistance. A blindfolded patient walking backward and forward will walk forward to one side and backward to the other, completely reversing his direction in from six to

eight excursions As a rule, the signs accompanying a lesion of the posterior fossa are sufficiently marked, either as a secondary hydrocephalus or critical evidence of involvement of the vermis, hemispheres of the cerebellum or cerebello-pontile angle to permit of differentiation

As careful observation of the differences of sensation as those of motion is necessary and often the response of "sharp" to the point of a pin may be made when considerable diminution of sensation exists It is important to note any difference upon the two sides as to intensity and quality alike. Although a painful effect may be obtained in lesions of the thalamus, the quality of sharpness is lost

Finally, a word about hemianopsia

The attention of a patient suffering from brain tumor often is exceedingly difficult to hold, and at times even pronounced hemianopsia is overlooked because of the seeming futility of securing any visual field examination Often form is recognized in the defective sector of the visual field in an imperfect manner, and asking the patient if he sees the examiner's fingers, especially if they are moving, may elicit normal responses If an object such as a glass of water is placed to one side of the patient with the vision of one eye obscured, while his attention is directed elsewhere, and he is commanded to take a drink, failure to recognize the presence of the glass of water in the blind sector of the field can be critically ascertained.

# The Psychological Panel in Diagnosis and Prognosis\*

## Correlation of Personality Type With Susceptibility to Disease, Based upon 1400 Necropsies.

By WALTER FREEMAN, M D , F A C P , *Washington, D C*

**T**O know an organ and its diseases thoroughly is the apparent goal of many medical and surgical specialists, but to know the patient thoroughly is the goal that should be set for himself by the true physician. All the great teachers have emphasized this, cautioning their students against too narrow a point of view. Nevertheless it is only with experience and practice, backed up by humanism, that the view can be broadened, since the intensive study of a particular disease or system of organs leads to the neglect of the larger aspects of the case and of the individual in which the disorder chances to occur. When the physician has cured the disease or seen the restoration of normal function in the part he may well consider that he has performed his office and that the patient will be satisfied. But there are many diseases that cannot be cured by topical treatment, and many conditions of disordered function that will not return to normal. Then the physician must study the patient as a whole, in-

vestigate him as an individual, adapting therapeutic procedures and laying down rules of life based upon a more certain knowledge of the patient's personality, obtaining cooperation by helping the patient to adjust to his new situation. The wise physician recognizes this, and the best physician is the best psychologist.

Psychology has more than therapeutics to offer the physician, however. Diagnosis and prognosis may occasionally be aided considerably by an insight into the patient's personality. There are correlations between types of personality and susceptibility to different diseases just as there are correlations between types of personality and physique (Kretschmer), and between physique and susceptibility to different diseases (Draper). My study deals with these psychologic-nosologic correlations.

Before indicating some of these relationships between personality and susceptibility to disease, it may be well to establish various types of personalities as they are encountered in the clinic and in the outside world. Upon a behavioristic basis men have been divided into many different groupings

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\*Read at the Minneapolis Meeting of the American College of Physicians, February 10, 1930

Thus such terms as extrovert-introvert, cyclothymic-schizothymic, syntonic-idiotropic, have come into common usage not only among psychologists and psychiatrists, but also among the laity. In dividing persons thus into two large classes, there are typical examples standing at either end of the scale, with graduations between by which one passes insensibly from one type to the other. Human nature, however, is not as simple as this. It does not permit classification by a single test. More than two groups are necessary, and yet with the multiplication of groups large underlying components are neglected and similarities go unrecognized. Four to six groups would probably best meet the requirements. The ones chosen in this work are four: Schizoid, Paranoid, Cycloid, and Epileptoid. It is my intent to show that these different personality make-ups are associated in no uncertain manner with susceptibility to certain diseases and resistance to others.

The material upon which this study is based is the autopsied population of St. Elizabeth's Hospital for a period of about ten years. The figures, strictly speaking, apply only to psychotic patients, but I maintain that psychotic individuals differ from normal people only in degree, and that the same psychologic trends can be found in mentally healthy individuals if they are sought. Certainly the earlier history of the patients in the institution very often indicates the development of behavioristic trends in one direction or another long before hospitalization became necessary.

## MENTAL REACTION TYPES

Individuals may be assigned to one or another of the four psychologic types by their manner of living and thinking. The schizoid individual is a shut-in dreamy person, timid, unambitious, fond of regularity and ritual in life, inoffensive, yet resistive to change even to the point of stubbornness. The paranoid individual is aggressive, arrogant, the kind that harbors a grudge and gets even. He explains his failures through the machinations of others, works hard, often bitterly, for appreciation, is ambitious, proud, sensitive, even suspicious, takes offense easily and makes friends with difficulty. The cycloid individual enjoys human companionship, is a good mixer, unreserved, emotional. He is easily depressed by misfortune but as easily gladdened by a good turn of affairs. Periods of tremendous industry often alternate with others of moody inertia. He functions best among people, makes snap judgments, is incapable of prolonged application, except when the task delights him. The epileptoid individual is affected by sudden unexplained outbursts of various types, especially convulsive seizures, but also headache, anger, asthma, etc. He is apt to be pedantic, devout, and often combines these features with some other peculiarity of personality.

Mixtures of these are often found, especially of the cycloid with paranoid characteristics, and often schizoid with paranoid elements, but it is usually possible to pick out the patients with one-sided psychologic characteristics. It is in regard to these that the data in this paper are most valid. In other words, a patient with pronounced schi-

zoid characteristics is much more likely to run true to form with regard to susceptibility or resistance to disease, than one whose characteristics are less well developed. The same is true of the paranoid or cycloid.

In dividing my own material into the four personality groups the principal psychologic trend has been the criterion. Accordingly there have been included not only typical cases but also many intermediate and borderline ones. The etiology of the mental disorder has been relegated to second place. I owe much to Dr. Nolan Lewis for sorting the patients into the various groups enumerated above. The distribution according to personality is shown in Table I. This may furnish a rough guide to the psychologic tendencies of the outside population, although the paranoid, and especially the cycloid individual may be more frequent outside the institution because he more seldom gets into disagreeable relations with the alienist and can more often convince a jury of his peers that he is mentally sound.

showed an overwhelming incidence in the schizoid group, while malignancy in all forms predominated in the paranoid group. Circulatory disasters and chronic streptococcal infections preponderated in the cycloid and paranoid groups, few of them appearing among schizoids or epileptoids. Intestinal catastrophes were fairly common in the schizoid group, and none at all were found in the cycloid group in spite of the fact that hernia was most frequent in this category. No instance of diabetes was encountered in the epileptoid group, and malignancy was rare. On the other hand, persistent thymus and cerebral malformations were very frequent in epileptics. Acute infectious diseases and deaths by violence showed little predilection for one or the other type. Most of these results have already been reported in a previous paper, but in the other tables is a list of morbid entities based upon further study of the material. The rates are per thousand individuals of each psychologic type.

This is not the place to discuss in

TABLE I DISTRIBUTION OF PERSONALITY REACTION TYPES IN PERCENTAGES

Race and Sex	Total cases	Schizoid	Paranoid	Cycloid	Epileptoid
White male	732	48.6	33.6	10.9	6.8
White female	189	44.5	35.0	13.2	7.4
Colored male	234	58.5	16.6	13.2	11.5
Colored female	186	49.5	21.5	15.6	13.4
Totals	1341	50.0	29.2	12.2	8.6

#### PSYCHOLOGIC-NOSOLOGIC CORRELATIONS

Further study of the individual groups indicated marked variations in susceptibilities to diseases of different categories. Tuberculosis, for instance,

detail the findings as indicated in the tables, since a complete study is in course of preparation. I do wish, however, on the basis of the tabulated findings, to stress the diagnostic and prognostic significance of an evalua-

TABLE 2. COMPARATIVE INCIDENCE OF CARDIO-VASCULAR DISEASES.

Disease	Cases	Schizoid	Paranoid	Cycloid	Epileptoid
Chronic myocarditis	98	41.8	125	109	25.9
Coronary thrombosis	56	22.4	92.0	30.3	8.6
Pericarditis, acute and chronic	50	14.9	74.0	54.6	17.2
Rheumatic Cardiac disease	74	38.8	102	72.8	51.7
Cardiac syphilis	49	23.9	33.2	72.8	69.0
Aneurisms luteic and senile	31	9.0	46.0	36.4	8.6
Vascular thrombosis excluding cerebral and coronary	45	29.9	53.6	12.1	25.9
Vascular ruptures excluding cerebral	20	7.5	28.1	18.2	8.6

The rates are per thousand of each psychologic type

TABLE 3 COMPARATIVE INCIDENCE OF NERVOUS DISEASES

Disease	Cases	Schizoid	Paranoid	Cycloid	Epileptoid
Cerebral hemorrhage	49	10.5	71.6	54.6	43.1
Cerebral thrombosis	192	76.3	238	188	147
Neurosyphilis	271	187	89.5	407#	380#
Infections of the nervous system	53	44.8	35.8	42.5	17.2
Pachymeningitis	45	31.4	33.2	42.5	34.5
Cerebral malformations	29	13.5	0	0	17.5

# The very high rates for neurosyphilis in these types are discussed in Am J Psychiat, 1928, 8, 425

TABLE 4 COMPARATIVE INCIDENCE OF RESPIRATORY DISEASES.

Disease	Cases	Schizoid	Paranoid	Cycloid	Epileptoid
Active tuberculosis	212	286	25.5	30.3	77.7
Tuberculosis (over 50)	86	223	21.2	37.8	71.3
Healed tuberculosis	132	68.7	143	109	103
Lobar pneumonia and influenza	107	88.2	69.0	66.7	86.1
Bronchopneumonia	470	287	352	534	475
Pulmonary infarction	55	23.9	56.3	48.6	60.5
Abscess & gangrene	48	35.9	33.2	36.4	43.1
Bronchiectasis	38	25.4	33.2	24.5	34.5

TABLE 5. COMPARATIVE INCIDENCE OF GASTRO-INTESTINAL DISEASES

Disease	Cases	Schizoid	Paranoid	Cycloid	Epileptoid
Peptic ulcer	30	17 9	27 6	48 5	0
Carcinoma of stomach	21	12 0	25 5	18 2	0
Intestinal tuberculosis	93	127	10 2	12 1	17 2
Hernia, all types	32	33 4	20 5	36 4	17 2
Intestinal gangrene	27	25 4	23 5	0	8 6
Foreign bodies	17	16 4	5 1	6 1	25 9
Chronic colitis	36	37 4	10 2	30 3	17 2
Cirrhosis of liver	42	20 9	46 0	42 5	25 9
Chronic cholecystitis with or without stones	232	127	266	176	121
Diabetes mellitus	13	12 0	7 7	12 1	0
Hemorrhagic pancreatitis	21	12 0	30 7	6 1	0
Biliary passages, Primary carcinoma	13	3 0	23 0	6 1	8 0

TABLE 6 COMPARATIVE INCIDENCE OF UROGENITAL DISEASES

Disease	Cases	Schizoid	Paranoid	Cycloid	Epileptoid
Nephritis, ac & chr	98	26 9	143	121	34 5
Arteriolar sclerosis	20	6 0	23 0	36 4	8 6
Pyelonephritis	53	34 4	48 5	60 7	8 6
Urinary lithiasis	22	7 5	38 3	12 1	0
Cystitis	69	50 8	57 0	66 7	34 5
Prostatic hypertrophy	95	60 8	175	108	38 9
Prostatic carcinoma	22	4 1	49 1	45 1	12 9
Uterine fibroids	120	307	321	444	205
Ovarian cysts	32	108	66 1	74 0	51 2
Urogenital malformations	22	23 6	7 7	6 1	17 2

TABLE 7 COMPARATIVE INCIDENCE OF ENDOCRINE DISEASES

Disease	Cases	Schizoid	Paranoid	Cycloid	Epileptoid
Pituitary tumors (small)	29	13 5	20 5	30 3	60 5
Goitre	86	59 7	76 6	84 8	25 9
Persistent thymus (20%)	45	16 4	10 2	12 1	190
Adrenal hemorrhage	19	14 9	15 3	6 1	17 2
Adrenal adenomata, and hyper-nephromata	37	29 9	23 0	30 3	25 9



TABLE 8 COMPARATIVE INCIDENCE OF PRIMARY MALIGNANT DISEASE.

Cases	Schizoid	Paranoid	Cycloid	Epileptoid
125	50 8	175	133	17.3

tion of the personality of the individual. This is particularly important in the proper diagnosis of obscure cases and the proper handling of outspoken cases. I refer especially to the differential diagnosis between tuberculosis and carcinoma when the physical signs are equivocal, and to the prognosis and treatment of individuals who show outspoken psychologic traits. A few case reports might be cited.

REPORT OF CASES

*Case 1* White male, aged 66 years, admitted to St Elizabeth's Hospital April 21, 1884, died April 24, 1926. Clinical diagnosis hypertrophied prostate, mental diagnosis dementia precox.

The patient became ill January, 1926, with fever, cough and expectoration. He was prostrated, but the cardiac sounds were of fair quality and the blood pressure was 164/78. Breathing was shallow, with moist râles posteriorly. A diagnosis of acute bronchitis was made, and the patient improved under appropriate treatment. It was noted later that urination was difficult. Rectal examination revealed a greatly enlarged prostate which was treated by massage, but a sudden rise of temperature on April 15th after two weeks of such treatment led to further examination. The prostate was greatly enlarged, drawn out to the sides, but not indurated as in malignancy. The median furrow was not felt. The catheter could not be passed. The seminal vesicles were not indurated. The urine contained a heavy trace of albumin and a heavy deposit of pus. The blood urea was 66 mg, per 100 cc. On April 22nd a suprapubic incision was made and a retention catheter introduced. Urinary suppression followed, however, and the patient died two days later. At necropsy a massive tuberculous abscess of the prostate was re-

vealed, with active lesions in the right kidney and early ones in the left. In addition there was acute tuberculous pneumonia.

The psychiatric record of the patient shows that he was admitted at the age of 24 in an excited state. Throughout his stay in the institution he was inaccessible, dull, apathetic, at times he was entirely mute, or exhibited peculiar mannerisms and postures, and took no care of his personal needs. This schizoid type of individual shows great susceptibility to tuberculosis and little to prostatic hypertrophy. Proper evaluation of the patient as an individual might have been the means of avoiding the dissemination of the tuberculous infection through massage of the tuberculous prostate.

*Case 2* Colored male, aged 46 years, admitted to St Elizabeth's Hospital July 29, 1908, died January 22, 1926. Clinical diagnosis not made, mental diagnosis, paranoid precox.

About January 14th the patient began to complain of pain in the abdomen, but showed no loss of weight or appetite. He refused to allow satisfactory examination, saying to the physician "Go away, I will have nothing to do with you." There seemed to be nothing requiring surgical intervention, and the temperature remained normal. About midnight on January 21st he cried out with a sudden sharp pain in his abdomen, which he said was as if something had burst within him. He was in severe shock, sweating, with some abdominal distension. An enema failed to produce relief and codeine was administered to relieve him of pain until operation could be performed. He died at 8 30 a m. Necropsy revealed an annular carcinoma of the descending colon with rupture of a greatly hypertrophied wall several centimeters above, the whole peritoneal cavity being filled with semi-fluid frothy feces.

The psychiatric record of the patient indicated that he was resistive, suspicious,

non-cooperative, occasionally noisy and dangerously assaultive. He believed that people were working against him, and he hated everybody. It is possible, had he permitted satisfactory examination, that the nature of the process would have been evident, but the character of the man should have awakened us to the possibility of carcinoma before the catastrophe occurred.

*Case 3* White male, aged 60 years, admitted to St Elizabeth's Hospital March 19, 1928, died June 27, 1928. Clinical diagnosis, coronary thrombosis, mental diagnosis, manic-depressive psychosis.

On June 20th, while out walking with other patients, he became suddenly ill, with subnormal temperature, pain in the chest, rapid pulse and vomiting. For the next few days there was slight fever and leucocytosis with abdominal distention but no tenderness or rigidity. The symptoms soon subsided, the vomiting did not recur and he became quite comfortable. He got out of bed, ate heartily, received visitors. Seven days later he dropped dead in a convulsion.

The earlier history indicated that the patient was arrested while directing traffic at a busy intersection. He had always been somewhat peculiar. At the age of 30 he became restless, moved about the country with his family, leaving job after job in quick succession. He was suspicious, meddlesome, complaining about his associates. In 1916 he had a period of depression and ceased supporting his family. Again in 1918 came a period of excitement that lasted for months and in 1927 a period of depression in which he became antagonistic, morose, suspicious. This resolved into the excited phase during which he was arrested. This type of individual, with his press of activity, his talkativeness, his meddlesomeness, is the one par excellence subject to circulatory disasters, and such was found to be the case at necropsy. The posterior wall of the left ventricle was reduced to a pulpy hemorrhagic mass, the surface was coated by a thin layer of fibrin, and there were thrombi in the left ventricle. Probably the coronary occlusion had occurred a week before death, and the terminal convulsion may have been due to ventricular fibrillation. The correct diagnosis was made in this case.

The point is, however, that it could almost have been predicted on the basis of his behavior, and preventive measures instituted.

*Case 4* White male, aged 80, admitted to St Elizabeth's Hospital September 19, 1924, died October 3, 1926. Clinical diagnosis, chronic myocarditis, bronchopneumonia, mental diagnosis, senile dementia.

Upon admission the patient was quite feeble, and spent most of the time in bed. His progress was uneventful, however, until August 12, 1926, when he became noticeably weaker and began running slight fever with rapid pulse and dyspnea. He recovered from the attack of acute bronchitis and did fairly well for nearly two months when the temperature rose to 104, the pulse to 140, breathing was very difficult, and he was evidently in extremis. The heart was slightly enlarged to the left without murmurs or irregularity, the arteries were sclerosed. Moist râles were heard over both lungs, without friction rubs, bronchial breathing, or change in the percussion note. The abdomen was scaphoid, no organs were palpable and no tenderness was present. The examination of the nervous system was negative. The patient died in less than 24 hours.

At necropsy there was found arteriosclerosis with myocardial fibrosis and dilatation. The left pleural cavity was obliterated by a thick, almost cartilaginous, pleura, white, rather translucent, with trabeculae of fibrous tissue running through it. There were milium nodules over the peritoneum, along the course of the lymphatics, and at the base of the mesentery. Similar nodules were found in the liver. The diagnosis at the table was flat tabular carcinoma of the pleura with metastasis. The microscope revealed tuberculosis.

Mentally the patient was confused, inattentive, disoriented. He showed marked loss of memory, talked in a rambling incoherent manner, lived in a dream world where the imaginary voices and visions were more real to him than the external world, and had no insight into his condition. The type of behavior placed him in the schizoid group, although the cause of the psychosis was arteriosclerosis and advanced age. Proper evaluation of his personality, together with

recognition of the manifestations of tuberculosis as seen in old age, should have aided me in making a correct diagnosis at the time of necropsy

The data given in the tables apply to psychotic people. If they apply as well to mentally normal individuals the physician's estimate of the patient's constitution and personality will aid him in his diagnosis and prognosis. The patient represents a unit, and to derive the most accurate information one must regard him as such, not as a collection of organs and an assembly of functions. Little of this is now heard in the clinic, dominated as it is by the laboratory and by instruments of precision. It must be recognized, however, that disease is the reaction of an individual to external or internal circumstances. Study of the individual as a whole will throw a light upon the fundamental nature of all his reactions. If he "lies down" when his boss upbraids him he is apt to lie down under the assault of the tubercle bacillus figuratively and literally. If he jokes about severe financial losses, he is apt to stand up well under severe hemorrhage or severe diarrhea. It is a question of "backbone." If he responds to a blow on the jaw by pinning his opponent's shoulders to the floor, his endothelial leucocytes may react to the insults of invading streptococci by penning them into a peripical focus in the same jaw. If he reacts to his discharge from a job by building up a series of delusions that destroys his insight, he also responds to physical injury by building up a new-growth that destroys his life. "Cancer," says Lewis, "is paranoia at the cellular level."

These ideas are not altogether fanciful. The basis for them is expressed in the tables. Too long has the clinician paid attention to the seed of disease and lost to sight the soil upon which it is implanted. The parable of the sower is more important to us in this day and generation than it was when Osler first uttered it, since it is being forgotten in the frenzied search for specifics and pathognomonics.

#### THE PSYCHOLOGICAL PANEL

How recognize psychologic types?

Some are instantly apparent; some are recognized in the first ten minutes; some not in ten hours or in ten years. It is in the ten-minute class that the foregoing data will be found most applicable. A few well-directed questions in regard to the past and social history of the patient will orient the examiner. These may be worked in without doing violence to the scheme of recording the history, and without distracting the patient. For instance:

Do you drink alcohol? How much?  
*How does it affect you?*

The answer to the last question will be much the most interesting, since the true character of the man is often made evident when the veneer of civilization and culture is dissolved off by alcohol. The cycloid is sociable, gay; the schizoid solemn, sleepy; the paranoid morose.

Have you had any accident? Any family reverses? *Do you blame other people or yourself when things go wrong?*

The schizoid blames himself, grieves in silence, hides his disgrace and waits for something to turn up. The para-

noid blames his boss, or believes his fellow-workers or some influence caused his reverse. As a school-boy, the teachers had it in for him. The cycloid is downcast, tells everybody of his hard luck, relaxes in alcohol or other diversion, then pulls himself together and runs for office or gets a job selling stock.

Have you had any venereal disease? Are you strongly sexed? *What is your attitude toward the opposite sex?*

The cycloid is often promiscuous, enjoys the society of the opposite sex. The schizoid idealizes or dislikes them; the paranoid holds them in contempt or shuns them (note the low rate for neurosyphilis). Yet all may be happily married.

*How do you get along with members of your sex?*

The cycloid has a large circle of friends, makes them easily, takes them at their own appraisal; the paranoid makes few, is suspicious though at times almost gullible, the schizoid is dependent upon one or two, or prefers to be by himself.

What is your occupation? *What hobby do you ride?*

A patient's avocation is frequently a guide to his character. Constructive arts appeal to the cycloid, reading and nature study to the schizoid, sports to the cycloid, his business to the paranoid. The collecting mania is seen in the schizoid and paranoid. Psychoanalysis explains the hoarding of old and useless things as a socially acceptable sublimation of anal eroticism. Wohlegemuth speaks of the psycho-ANALISTS.

Are you worried over your business or finances? *What would you do if*

*somebody gave you a hundred thousand dollars?* (This is a favorite question of Howland's.)

"Go round the world," says the cycloid, "buy a house; buy a car; get married." "Pay my debts; invest it, buy a lot of clothes, take a course," says the schizoid. "See my lawyer," says the suspicious paranoid, or "buy out the boss."

Are you easily depressed? Are you suspicious of others? Are you easily embarrassed? Are you religiously inclined?

Ten minutes sympathetic questioning of a cooperative patient will bring out sufficient material to give the examiner a lead to the manner in which the patient reacts to his environment. Then an appraising glance at the physical make-up of the patient may supply corroboration. The cycloid is apt to be thick-set and ruddy, the schizoid pale and thin, the paranoid well-developed muscularly, the epileptoid often disproportioned. Such a comparison of head, trunk, and limbs in the same individual will tell more at a glance than will a host of separate measurements. Again the individual must be regarded as a unit.

Somewhere in his notes the physician should enter his impressions concerning the personality make-up of his patient, and should recall these impressions in his summary of the case, and in his diagnosis, prognosis and therapeutics. When he does that he will rise above the stage of treating a disease and find himself treating the patient. The best psychologist is the best physician.

## CONCLUSIONS

Life is a constant interplay of action and reaction. External influences impinge upon the individual and he reacts to them more or less specifically, in a manner determined by his organismic pattern. If he reacts in a particular manner to a psychologic insult, he will react in an analogous manner to a bacterial or to a chemical insult.

Some correlations between personality reaction type and disease susceptibility are indicated. By a study of the personality of the patient some insight may be gained into the manner in which he reacts to other situations. Diagnosis and prognosis, as well as therapy, depend upon knowing the patient.

# Gastro-intestinal Troubles That Now Go Undiagnosed\*

WALTER C. ALVAREZ, M.D., *Division of Medicine, The Mayo Clinic, Rochester, Minnesota*

FOR years I have been distressed at my inability to label with the usual textbook tags a considerable number of the patients who complain of indigestion or abdominal distress. Some of the fault is doubtless mine but much of it I feel sure is due to the fact that as yet the textbooks have not supplied me with all the tags I need. "Authorities" are notoriously conservative, and particularly so when it comes to the classification and naming of disease. For years the surgeon with his exploring knife has been playing havoc with old ideas, he has shown that cholecystitis and duodenal ulcer are common and gastritis and gastric ulcer are rare, but years go by before the writers of books surrender to the new diseases the pages so long devoted to the old.

For a generation we have known that the stomach is not the essential organ of digestion and that organic disease of its walls is rare, and yet, so great is the conservatism of publishers that they persist in labeling their textbooks on gastro-enterology

with the old title of "Diseases of the Stomach." The commonest single cause of severe indigestion is probably disease of the gallbladder but if one turns to a "System of Medicine" and looks for cholecystitis where one would expect to find it, in the volume on "Diseases of the Stomach," it will probably not be there. Why? Because in the old scheme of things the gallbladder belonged with the liver, and there it still is, treated in a more or less stepmotherly way. There one can find much about gallstones but little if anything about the problems which daily confront the modern consultant. Where except from his own experience and the perusal of contemporary journals can he learn anything about the real significance of what the pathologist rather grudgingly calls "slight cholecystitis," or where can he learn something that will help him in handling the patients who after cholecystectomy continue to have colic or symptoms suggestive of biliary tract infection?

## A SEARCH FOR NEW SYNDROMES

Obviously, if we who are puzzled are ever going to get any new information we must dig it out for ourselves. We must study disease in our

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patients and not in our books. In the years in which I have practiced medicine I have watched several new syndromes emerge from the group of so-called neuroses, and I see no reason why the process should not continue. Twenty-five years ago such troubles as duodenal ulcer, early cholecystitis, and chronic ulcerative colitis were rarely recognized, twenty-five years from now those of us who are still alive will be wondering how it was that in 1930 we could have failed to see that certain of our cases fall into definite groups, and that the symptoms of the patients were too severe to be accounted for on the basis of a neurosis.

Obviously, then, we must go looking for new diseases; but where? Explorers do not hunt for new land in the Mediterranean; they conserve their energies by hunting only about the Poles or in New Guinea or Tibet. Where should we be hunting? In the hope of throwing light on this question, I took from my files the records of 500 patients (227 men and 273 women) who in the latter half of 1925 in San Francisco consulted me in regard to indigestion or abdominal distress. I chose these cases for several reasons one, that I had studied them personally, another, that in many instances I had known the patient for years, or long enough to become well acquainted with the problem involved, and another, that I wished first to get some idea of the experience of an ordinary consulting gastro-enterologist. Later with the help of my colleagues I hope to analyze more of the strange problems which

are fairly common in a large institution like The Mayo Clinic.

#### DIFFICULTIES IN CLASSIFICATION

As soon as the records were read and abstracted, it became obvious that in many cases it would be impossible for anyone to make a single clear-cut diagnosis. It is comparatively easy to do this when all the complaints of the patient are clearly related to the presence of some serious lesion such as peptic ulcer or cholelithiasis, but how is one to classify the indigestion of a nervous, psychopathic woman with migraine, constipation, mucous colitis, urticaria, hypertension, gallstones, uterine fibromyomas, and a husband with whom she cannot live in peace. I am thinking of an actual case in which the first therapeutic experiment was the removal of the gallstones. As this produced only temporary improvement the foods which were causing the urticaria and possibly some of the attacks of mucous colitis were next detected and eschewed. Again there was a little improvement but the woman continued to be prostrated by severe attacks of headache, abdominal pain and vomiting. To make peace in the family the husband then left home but this didn't help much. Finally as I came to know this woman I saw that her troubles were due almost entirely to the severe migraine, the stones were impressive to look at but apparently they had been silent and had had little to do with the case. I have therefore listed her record under the heading of migraine. The point I wish to make is that if I had lost track of the woman in the first few months after the oper-

ation when she and I thought it had cured her, I could have classified her case as one of cholelithiasis

Perhaps the strongest impression which I have gained from the study of these 500 case histories is that today the poverty of our knowledge in regard to the more unusual types of gastro-intestinal disease is due largely to the fact that we physicians so often see but one short episode in the course of a long-continued chronic disease. Let us say that a woman has wakened at 2 a m with nausea, vomiting, and abdominal pain, a few days later the digestive tract appears by every test to be normal, so a few suggestions are made as to the diet, perhaps a little rest is prescribed, and the patient departs. Was it an attack of food poisoning or a manifestation of some serious disease? Six months later when another attack comes this time with an accompaniment of jaundice, melena, blood in the urine, or choked discs, the patient goes perhaps to another physician and the ignorance of the first remains unchanged.

For a number of reasons, then, the proper classification of many of the cases listed in table I is impossible. The grouping which I have attempted, although obviously imperfect, will, I think, be helpful in that it gives some idea of the extent of the problem which needs now to be attacked. The groups are made up of persons with (1) definite disease of the gastro-intestinal tract, (2) symptoms suggesting such definite disease, (3) disease in organs outside the digestive tract, (4) generalized diseases, (5) nervous troubles and constitutional handicaps, and (6) poorly understood

symptoms such as constipation, diarrhea, and flatulence

#### DEFINITE DISEASE OF THE GASTRO-INTESTINAL TRACT

The first point to be noted is that a definite diagnosis of disease of the digestive tract was made in 175 or about one-third of the cases. The commonest single cause of indigestion seemed to be cholecystitis, with or without stones. About half of the seventy-seven patients were operated on and the diagnosis confirmed. It was interesting to see how many of these patients were suffering also with hypertension, heart disease, fibromyoma of the uterus, and arthritis. As F. H. Carber recently pointed out to me, these diseases which accompany cholecystitis have great significance not only because they keep the patient from recovering completely after cholecystectomy but because they shorten life.

The next frequent cause of trouble was duodenal ulcer, and after this the next was subacute or chronic appendicitis. The diagnosis of appendicitis was made conservatively and in almost every case the criteria were first, that the patient had had typical or fairly typical attacks, and second, that if operation was performed recovery was definite and lasting. As will be noted, gastric ulcer and gastric carcinoma were rarely encountered.

I have included in this group of patients with organic disease four cases of infestation with *Ameba dysenteriae* and two of heavy infestation with *Giardia lamblia*. Such parasites can often be found in the stools of patients but my impression is that in



most cases they have little if anything to do with the production of the symptoms complained of. Hopefully one prescribes the appropriate drugs, the cysts disappear, but too often the patient returns with the same old troubles. For one success I have had many failures. I sometimes tell patients that in my estimation their few intestinal parasites are like a few fleas: undesirable of course, and nice to part with, but not the cause of their neurasthenic symptoms.

A number of authorities deny that giardiasis ever produces symptoms but in the two cases listed in table I the recovery after treatment was so striking that the inference is that the organisms were pathogenic. There was one additional case of great interest in which an athlete suddenly found himself, in the middle of the training season, too weak to run. As I had just cured his sister of years of indigestion by ridding her of *Giardias*, his stools were examined and found to be full of cysts of *Ameba dysenteriae*. While these were being removed, the stools became filled with cysts of *Giardia* and when those were also wiped out, the boy was soon winning races again. Because *ameba dysenteriae* is the more definitely pathogenic organism of the two I have, in table I, classified this case as one of amebiasis.

I must admit, of course, that the sister's trouble may have been due to an unrecognized amebiasis which was cured by the salvarsan used to destroy the *Giardias*, but this is the difficulty which dogs the steps of everyone who would attempt to bring order out of chaos in the field of gastro-intestinal

pathology. I can remember how in my medical youth I read with interest articles on such topics as "The indigestion of the menopause." Today I would not even look at them unless the writer could assure me that in each case he had, by exploration at laparotomy or necropsy, ruled out the presence of organic disease, particularly in the biliary tract.

There is many an article on, let us say, gastric hemorrhage in chronic appendicitis which would never have been written if the author had spent more time watching necropsies. I do not mean to imply that there is no such thing as gastrorrhesis in appendicitis, the point I am making is that anyone who elects to write about such conditions should know how frequently silent peptic ulcers are found at necropsy, and how difficult it is for a surgeon at operation to make sure that there is no lesion on the posterior wall of the duodenum.

Two cases listed in table I under the title of chronic mesenteric lymph-node disease interest me greatly because I believe they represent one of the new syndromes which I now want to see studied. The subject has recently been discussed by Freeman. The symptoms in a number of my cases were attacks of nausea and diarrhea, with abdominal soreness, sometimes fever, and usually much prostration and nervousness. I think it probable that future research will show that there are several causes for the large nodes. One of them may be infection with *Brucella abortus*. In some of my cases tuberculosis was suspected and in others it was ruled out.

There is another condition to which I would like to call attention and this is inflammation and widening of the anal ring. Among the 500 cases there were three in which I deemed this to be the basis for abdominal discomfort, constipation and flatulence. Certain it is that as soon as a proctologist cleared up the inflamed crypts, fissures, and small fistulas, the symptoms all disappeared and the bowels moved normally again.

There were two interesting cases in which cholecystitis was probably part of a generalized infection with some organism of low virulence. In one there was fever and arthritis which lasted for two years. Some features suggested tuberculosis but its presence could not be demonstrated. In the other patient the organism was a streptococcus of viridans type which, during the course of years, invaded one organ of the body after another. I believe that many of the curious abdominal troubles that are associated with tenderness of the liver, symptoms suggesting cholecystitis, occasional slight rises in temperature, and sometimes arthritis, are due to smouldering generalized infection with organisms of low virulence.

#### PATIENTS WITH SYMPTOMS SUGGESTING ORGANIC DISEASE

This group is to me the most interesting of all because it is the one in which research is most needed. It comprised 115 patients or over one-fifth of the total number. Many were incapacitated or were suffering so much that the trouble could hardly be ascribed to nervousness. In sixty cases the clinical picture resembled

that of cholecystitis, but for a number of reasons, the diagnosis remained in doubt. In some, important symptoms were lacking, or the patient was so querulous or so self-contradictory that the history could not be taken at face value. In others the gallbladder concentrated well with the dye test, or at operation the organ did not appear to be diseased. In a few the gallbladder was thought at operation to be diseased and was removed, but later, doubt crept in because the patient failed to improve.

Such cases in which after operation on the gallbladder the patient continues to suffer with the old symptoms of bloating, colic and perhaps even jaundice are very trying to the clinician. If stones were found at the operation or if the gallbladder was only drained, it often pays to operate again to look for more stones or to remove the gallbladder, but if the organ never contained stones, if it was removed, or if there is no jaundice, there is little to be hoped for from another laparotomy.

In many of these cases it seems to me that the symptoms must be due to the persistence or recurrence of infection throughout the biliary tree, and a tendency to spasm in various parts of the digestive tract. So far as I know no one has as yet offered any explanation for the troublesome flatulence complained of by these patients. Many of them doubtless continue to suffer because they are neurotic, or because they are handicapped by hypertension, migraine, or the nervous upsets that attend the menopause.

The diagnosis of peptic ulcer is not always easy. In eight cases the roent-

genologist saw a defect in the duodenum but either the symptoms were indefinite or they failed to respond to the usual treatment for ulcer. In a clear-cut case everything points the same way: symptoms, high acids, cap defect, relief with two hourly feedings, lesions at operation, and cure after gastro-enterostomy, but in the puzzling cases there are strange contradictions in the evidence. Thus in one instance the symptoms were characteristic of ulcer, the roentgenologist saw a defect in the outline of the gastric shadow, and at operation the surgeon felt a thickened area which he excised. The pathologist, however, could not, in the tissue which he received, find any ulcer, and the patient continued for years to suffer with hunger pain.

Eight persons suffered pain and distress in the region of the appendix, but, again, I could not always be sure of the diagnosis even when operation brought relief. The difficulty was that I soon lost track of the patient, and a cure lasting a few months failed to impress me. What happened after that would have interested me more.

There were sixteen patients in whom the only diagnosis possible was the meaningless one of abdominal pain. Perhaps in some of them a real diagnosis could have been made if I had been able to observe the patient long enough or if I could have seen an acute attack.

A troublesome group of cases is that in which after appendectomy the patients continue to complain of pain and distress in the right lower quadrant. In some of them I suspect that the trouble is due to a persistence of

low grade infection either in the walls of the ileum and cecum or in the glands draining this region. A few of these patients have a sort of hunger pain which occasionally is relieved by food, perhaps because eating helps the terminal ileum to force its contents past a spasmodically contracted ileocecal sphincter.

In one such case in which for several years the patient had been incapacitated by pain and vomiting, and in which on roentgen-ray examination I found marked ileal stasis and some gastric stasis, Dr C H Mayo short-circuited the ileocecal sphincter by making a new opening between the ileum and the ascending colon, and obtained a perfect and lasting result. Spasm of the ileocecal sphincter probably serves as the basis for at least one of the syndromes which some day will be recognized and dignified with names.

I have placed in this group of puzzling cases those with diverticulitis of the colon because although it is easy to demonstrate diverticula it is not always so easy to say that inflammation is present in some of them and that this inflammation is responsible for the symptoms complained of. I have seen cases in which the discovery of harmless diverticula so fully satisfied the clinician that he failed to look further and thus missed the really important lesion in gallbladder or stomach.

There are a number of cases in which I strongly suspect that the indigestion of later life is a sequel of peritonitis in childhood or youth: peritonitis which left adhesions and loci of minor resistance.

I suspect that there are cases in which early cirrhosis or other disease of the liver with resultant disturbances of the portal circulation must produce indigestion and abdominal distress, but as yet the syndrome has not been recognized. Probably, in most cases, if any diagnosis is made it is that of cholecystitis.

I have listed two cases under the heading of gastritis or enteritis but I have placed a question mark after these diagnoses because if a necropsy could have been performed it might have been impossible to demonstrate changes in the mucosa. One case was that of a woman who was well until she ate some sandwiches at a picnic. Shortly afterward she suffered with intense pain in the epigastrium, with a burning feeling there, and globus. In the weeks that followed she lost 22 pounds in weight. In the other case, a similar upset followed an attack of "influenza."

I have encountered a number of instances in which after an acute attack of "food poisoning" or more probably of infection of the digestive tract with pathogenic organisms, symptoms of indigestion continued for weeks and months until the amount and quality of the food was restricted and the digestive tract was given a rest. Recent studies by Childrey at the Mayo Clinic have shown that if the intestine is overburdened and overwhelmed on one day it will not digest well on the next. Under such conditions a vicious circle may easily be started and maintained unless, for a few days, the work of the bowel is made easy.

#### DISEASES IN ORGANS OUTSIDE THE DIGESTIVE TRACT

In four cases the abdominal pain complained of appeared to be due to arthritis of the spine, with involvement of nerve roots. Such spondylitis, with a history of previous lumbago, wry neck, or sciatica, was encountered in twenty-four other cases but in them the relation of the disease to the abdominal discomfort was not so clear.

In many of the women it seemed to me highly probable that the tendency to indigestion was related in some way to the presence of defective ovaries, old pelvic inflammation, a retroverted uterus, or uterine fibromyomas. I have always had the impression that there is a relation between cholecystitis and pelvic disease but it would take a careful statistical analysis of necropsy records to prove it. Of one thing I am certain and this is that it will repay the gastro-enterologist to consult frequently with a good gynecologist.

In one case a puzzling pain in the hypogastrium which had been ascribed by several physicians to diverticulitis, inguinal hernia, and appendicitis was relieved as soon as posterior urethritis was discovered and treated. In another case the distress which had been thought to be digestive in origin was relieved by the removal of a large prostate.

Some physicians may be surprised to find that I have listed only two cases in which the cause for the indigestion was assumed to be dental infection. In many instances I suspected that severe pyorrhea was an important factor but other causes for the symptoms could always be found, and doubt remained in my mind. In one case the

indigestion and nervous breakdown of a husky farmer was traced to osteomyelitis in the mandible, in the other, the patient, a big lumberjack, had for several months been going from physician to physician seeking in vain for relief of symptoms which suggested the presence of peptic ulcer. No one had been able to demonstrate such a lesion, and the usual Sippy treatment did not give relief. On general principles I had two badly decayed molars removed, and to my surprise the man returned in a few days to say that his symptoms were gone, his strength had returned, and he was off to the mountains again.

#### GENERALIZED DISEASES

In twenty-six cases it seemed to me that the complaints of the patient could best be accounted for by the presence of hypertension. I do not mean that hypertension ordinarily produces indigestion; often in the most severe forms it does not, but occasionally it causes the victim to seek the advice of a gastro-enterologist because anginoid pain, extrasystoles, paroxysmal tachycardia or the distress occasioned by a failing heart are thought to be due to the accumulation of gas in the stomach.

A number of elderly patients who for some time had been treated for indigestion but who really had a failing heart were miraculously cured as soon as I induced them to move away from San Francisco's steep hills. In elderly persons with hypertension, attacks of dizziness with nausea and even vomiting must often be due to tiny thromboses of the vessels of the brain or to transitory shut-offs in the cerebral circulation. I have seen physicians

make a diagnosis of "acute indigestion" when a little examination of the patient would have revealed a slight hemiplegia.

It would seem that some of the indigestion and flatulence of persons with arteriosclerosis and hypertension must be due to disturbances in the blood supply to the bowel and to other abdominal organs, but as yet I know of no way of telling when such disturbances are present and responsible for the symptoms complained of. Research along these lines should be profitable.

In four of the 500 cases the cause of the indigestion was an unrecognized pulmonary tuberculosis. In three there was hyperthyroidism, and in one myxedema. In one case the subsequent history showed that I had been dealing with the beginning stages of a rapidly fatal leukemia, and in another I strongly suspected that I was face to face with the early symptoms of pernicious anemia. In still another I feared that I was dealing with some lesion of the suprarenal glands. The woman had been heavily exposed to tuberculosis in childhood, there were calcified nodes near the left kidney, and the skin was suspiciously dark. At intervals of one or two weeks she would suddenly be prostrated by an attack of nausea, severe diarrhea, sometimes abdominal pain, and always that shaky nervous feeling which is experienced after an overdose of epinephrin. Unfortunately, I never had a chance to study the blood pressure in an attack. She recovered after a long course of heliotherapy.

### NERVOUS TROUBLES AND CONSTITUTIONAL HANDICAPS

In thirty cases I have used as a diagnosis the term "fatigue neurosis" It is fairly satisfactory in that it brings to mind the picture of a man or woman who has broken down under the strain of overwork, long hours, heavy responsibility, no vacations, and perhaps insomnia It is unfortunate that nowadays so many of these patients, instead of being given the rest which they so sadly need, are driven "over the edge" into a nervous breakdown by ill-advised operations for the removal of teeth, tonsils, or appendix Even when definitely indicated, such operations should, I think, be deferred until the patient has had a chance to rest

When there is no history of overwork and yet the patient is obviously hypersensitive, apprehensive and on edge I use the term "nervousness" Many persons resent this word because they think it implies that they are excitable, flighty, foolish, or in some way culpable They forget that a person who is outwardly calm may be inwardly seething, tense, and frightened

I have coined the word "temperamental indigestion" to describe the troubles of certain men and women, often of one of the Mediterranean races, who get along well enough until some annoyance sets them off into an emotional debauch The term "anxiety neurosis" is useful to describe those cases in which, after the sudden death from cancer of a relative or friend, or after a visit to a pessimistic or tactless physician, or after the appearance of symptoms which are thought to be due to the return of an

old well-treated syphilis, the patient becomes terror-stricken

I usually place in a special category those persons who are living under terrible strain and who are eating their meals to the accompaniment of bitter words Perhaps the wife is insanely jealous, or the husband has been untrue and a divorce is pending, but whatever the reason, there is little that the physician can do until peace is restored

I believe there should be a separate classification for the women who vomit or regurgitate immediately after meals The problem is not one of indigestion because the food which is retained is handled comfortably, and operations on the stomach or bowel are worse than useless In one case recently studied by R. L. J. Kennedy and me the difficulty was not in the stomach at all but in the left leaf of the diaphragm where a violent tic-like contraction appeared as soon as food was taken

In table I I have grouped together those persons who seemed to me to be psychopathic, "constitutionally inferior," asthenic, or deficient in ovarian function Gastro-enterologists would do well to remember that for every insane person confined in an asylum there are several queer, poorly adjusted relatives at large, and many of these complain of indigestion, "auto-intoxication," depression, or weakness which is out of all proportion to the amount of physical abnormality that can be found In these cases the physician will do well to focus his attention on the weakness and the inability to stand up to the strain of life

and not on the aches and pains in the abdomen.

I think the term "constitutional inferiority" is a useful one with which to picture the thin, nervous, flabby, weak-backed, poorly sexed girl who, if she had been born a kitten or a puppy would not long have escaped drowning. Some "asthenics" could doubtless be placed in this group but I reserve for them a less opprobrious term because so many, though physically handicapped, drive onward with such keen, active, idealistic brains that they succeed in doing much of the constructive work of the world. I have never been able to decide whether they are tired because they were originally endowed with too little strength, or simply because they spend what they have so recklessly in an effort to do three men's work in a day.

I place in a separate group those women who show a masculine type of distribution of hair on face, breasts, and abdomen, and who have defective pelvic organs, painful and scanty menstruation, and sexual anesthesia. For the sake of brevity I continue to label this polyglandular defect with the term "hypovarianism." Many of them suffer with nervous indigestion, mucous colitis, and constipation.

Years ago I would have classified a number of the thin congenitally handicapped patients as victims of enteroptosis but now that I know how commonly this condition is found in healthy persons, I doubt the wisdom of ascribing symptoms to it. Some persons doubtless feel better while wearing an abdominal support but this does not convince me that enteroptosis is a disease. The good which these

women often derive from a sojourn in a sanitarium is due probably not so much to the fat which they put on as to the rest which they get. I think I would as willingly ascribe symptoms to a large navel, to a hooked nose, or to flaring ears, as to a mobile cecum or to a redundant sigmoid flexure.

I fear that many physicians do not yet know the danger of operating on patients with severe migraine. The attacks of nausea, vomiting, prostration, and severe abdominal pain may strongly suggest the presence of cholecystitis, but the expert will continue to question the patient until he is sure that there is never any indigestion between attacks, and never an attack without headache. If the cerebral disturbance always comes first he will know that operations must not be done. I have seen patients with this disease who have submitted cheerfully to one useless operation after another; usually first appendectomy, then cholecystectomy, then gastro-enterostomy, and finally the taking down of the gastro-enterostomy. Surgeons must learn that in these cases it is useless to open the abdomen because the disease is not there. It is probably up in the brain from whence there spreads out down the vagi or splanchnics a nervous "storm" similar to that which produces the abdominal crises of tabes. Even when gallstones are found their removal may have no effect on the course of the disease. It is possible that some of the cyclic vomiting and other poorly explained digestive upsets of children represent "migraine equivalents".

Mucous colitis is another condition which accounts for much unnecessary

opening of the abdomen At operation I have looked at the colon in some of these patients, in others I have sectioned it, and studied the slides under the microscope, and I have been unable to find anything wrong I have seen the surgeon remove half of the colon and cure the constipation which was thought to be the cause of the mucous colitis, and still the patient continued to lie on a couch with a hot water bottle over the place where the cecum used to be

It seems to me obvious that the disease is not a true colitis There exists first a congenital predisposition; second, a hypersensitiveness to many types of stimuli, and third, perhaps some local source of irritation, as in the pelvic diseases of women Research is much needed in order to learn what happens to intestinal secretion and absorption during an attack

In some cases, perhaps in many more than we now suspect, abdominal distress is due to hypersensitiveness of the colon to certain foods, or perhaps to substances which are excreted through its wall Spectacular cures can sometimes be obtained when the offending foods are detected and avoided, and in a few cases I have even seen headaches disappear

The difficulty in recognizing these cases of so-called "intestinal allergy" is increased by the fact that urticaria is not always a part of the clinical picture The points that should arouse suspicion in the mind of the medical attendant are that the patient or one or more of his or her relatives are subject to hay fever, asthma, or eczema, and that the attacks of abdominal distress are associated with irritability of

the bladder, with pain in the muscles and joints, and perhaps with hives and headache

For a time I wondered if this type of sensitiveness might be the cause of mucous colitis, but observations made by intelligent patients have convinced me that although "intestinal allergy" may at times give rise to an attack of "colitis" the two conditions are sufficiently distinct so that those who suffer with both diseases can tell them apart A woman who has learned to avoid all the foods that used to poison her tells me that she still has attacks of mucous colitis whenever she gets a cold, when she becomes greatly fatigued, or when she loses her temper

I do not like the way in which many physicians now apply the term colitis to every case of spastic constipation in which the haustration of the colon is a little irregular I think the term should be reserved for those cases in which, with the sigmoidoscope, one can see that the mucous membrane is definitely inflamed or ulcerated

#### SYMPTOMATIC DIAGNOSES

In nineteen cases the only diagnosis made was constipation. There are many patients in whom flatulence and indigestion can be relieved if only the lower end of the colon can be emptied without insult to the rest of the bowel When the colon is highly sensitive, purgatives and rough diets are equally injurious, and often then the best solution of the problem can be found through the use of enemas of warm physiologic saline solution

I dislike the usual textbook division of constipation into spastic and atonic varieties because I doubt if there is any



basis for it in fact. I think it more helpful to divide the cases into (1) those due to nervous strain; (2) those in which the stasis is rectal, (3) those in which there is stagnation in a large cecum, (4) those in which the cause is probably cholecystitis, pyloric obstruction, or chronic appendicitis; (5) those in which the food is insufficient in amount or in residue; (6) those in which there is disease about the anus or in the pelvis, (7) those in which the disturbance is due largely to neglect of the calls of nature, and (8) those in which it is due to carcinoma of the bowel or to diverticulitis.

There were thirty-six cases of diarrhea. As Cabot long ago pointed out it is seldom that one can, even with the help of all modern diagnostic methods, hazard an explanation as to the cause of diarrhea. When ova and cysts of pathogenic organisms cannot be found, when gastric acidity is up to standard, when the bacterial flora is within limits of normal, and the colonic mucosa unbroken what is one to say?

I have classified one patient as an air-swallower because he was so unusually good at it, but when I fitted this tag to him my responsibility did not cease; I had still to explain why he wanted to belch, and why he kept up this fatiguing practice hour after hour. In many cases it is a tic or habit spasm dependent on exaggerated reflexes which are mediated by a hypersensitive, tired, over-worked brain and cord, but in others the cause is to be found in a diseased gallbladder which upsets the normal rhythm of the gastric waves, or in a hypertension with its attendant failing heart.

The last case on the list was an interesting one. It was that of a very tall thin young woman who had learned the trick of noisily swishing water and air from one end of her long stomach to the other. When it was pointed out to her that this was not a disease but only an accomplishment of doubtful social value she lost interest in it.

#### MINOR DIAGNOSIS AND INTERESTING SYMPTOMS

It will be remembered that as I abstracted the records of the 500 cases I made note in each instance, not only of what I considered to be the principal diagnosis but also of other less important ones, and even of some of the outstanding symptoms. When these were listed the resulting table was so large that I thought it best to abridge it and present here only the more important and interesting items.

That the clinician should have a thorough understanding of cholecystitis and all its attendant problems will be seen from the fact that this condition was diagnosed definitely in eighty cases and its presence was suspected in ninety-five more. The tremendous importance of nervousness in gastroenterological practice can be seen from the fact that in at least 109 cases it had to be considered as a factor in the causation of the patient's illness. Hypertension is another important condition. It was considered to be the most important one in twenty-six cases but it was pronounced enough to be mentioned in another sixty. Disorders of the heart were found in thirty-one. Diarrhea was mentioned in the histories of seventy-two patients. Seventeen persons had a low basal metabolic

rate and one was definitely hypothyroid

Duodenal stasis was noted in four cases but in none of them was it considered pathogenic. Diverticula of the duodenum were found occasionally but in one of the cases did the condition appear to be responsible for symptoms.

I was puzzled by four women who complained of a disturbance in the sense of taste. In some it was salty, and in others it was acid or bitter. In some the disturbance was unilateral, but what it was and how to cure it I never could learn. I read widely but found nothing that gave me light.

### CONCLUSIONS

It should be obvious from this study that further research is needed, particularly in the group of cases in which the symptoms are severe enough to suggest the presence of organic disease of the digestive tract but in which the nervousness of the patient, the way in which the history varies with repeated telling, the absence of certain important features, the absence of roentgenologic signs of disease, and perhaps the inability of the surgeon to find anything wrong at operation makes a satisfying diagnosis impossible. In some of these cases the symptoms may possibly be due to disease in the brain, in the cord, in the nerves supplying the viscera, or in the blood vessels going to them.

There is no question that disease of the brain and cord can simulate acute cholecystitis or appendicitis. Supposed pathologic changes have been found in the nerves and ganglions connected with the digestive tract but it is so difficult to stain nervous tissue and

then to interpret what is found that I do not know what value to put on the reports so far available.

Some of the necessary advance in knowledge will probably come through better follow-up studies of patients with strange symptoms; others will come when we physicians have a better understanding of the physiology and bacteriology of the bowel, and others will come through more careful and minute studies of the tissues obtained at necropsy.

I think it should be obvious also from this study that no one can be a good gastro-enterologist until he has first become a good clinician with a wide knowledge of disease of every kind, in every part of the body.

### SUMMARY

This paper represents an analysis of the diagnosis made in 500 cases of indigestion with abdominal discomfort. The study was made with the idea of mapping out the areas in which clinical research is most needed.

In 175 cases, or in one out of three, there was organic disease of the digestive tract. In fifty-two cases the cause for the symptoms was found in organic disease outside the digestive tract. In ninety-five cases the patients were congenitally handicapped or nervous and the symptoms seemed obviously to be functional in origin.

The most puzzling group was made up of 115 cases in which the symptoms were so severe as to suggest the presence of organic disease. The syndrome often resembled that of cholecystitis but frequently it suggested the presence of ulcer or appendicitis.

Cholecystitis is the most common single cause for severe indigestion.



	Cases		Cases
Alternating constipation and diarrhea	1	Aerophagy	1
Flatulence	5	Gastric borborygmus	1
Diarrhea	36		—
			158

TABLE 2 PRINCIPAL AND MINOR DIAGNOSES TAKEN TOGETHER\*

Cholecystitis	69	Pulmonary tuberculosis	
Cholelithiasis	11	(active or healed)	10
Duodenal ulcer	43	Tuberculosis suspected	5
Gastric ulcer	5	Hypertension	88
Appendicitis	33	Heart disturbances	27
Cholecystitis suspected	90	Paroxysmal tachycardia	4
Cholelithiasis suspected	5	Hypothyroidism,	
Duodenal ulcer suspected	22	usually moderate	18
Ulcer suspected	9	Migraine	25
Gastric ulcer suspected	2	Migraine questionable	5
Appendicitis suspected	24	Headache	11
Post-appendectomy pain	6	Arthritis, cervical	3
Duodenal stasis	4	Arthritis, spinal	23
Diverticulum of the duodenum	3	Arthritis, generalized	9
Allergy	26	Sciatica	2
Allergy suspected	5	Constipation	43
Amebiasis	12	Diarrhea	72
Ameba coli infection	7	Flatulence	16
Inflamed anal ring	10	Strange taste in mouth	4
Calcified nodes in the abdomen	9	Mucous colitis	8
Pelvic disease in women	43	Mucous colitis questionable	4
Menopausal upset	6	Nervous troubles	109
Fibromyoma of the uterus	30	Nervous vomiting	4
Hypovarianism	20	Psychopathy	11
Nasal sinusitis	5	Asthenia	5
Tabagism	3	Constitutional inferiority	13

\*A patient whose case was classified in table 1 as one of cholelithiasis may have had in addition duodenal ulcer, hypertension, and pelvic disease. In table 1 the case was listed under one heading, here it is listed under four.

# Arteriosclerosis in Diabetes\*

By ELLIOTT P. JOSLIN, M.D., *Boston*

EVERY other diabetic now dies of arteriosclerosis and the percentage of such cases has been rapidly rising. In the Naunyn Era it was 15 per cent, in the Allen Era 26 per cent, in the first half of the Banting Era it was 41 per cent, but for the last 4 years in 781 fatal cases in my own series it has grown to 50 per cent. In diabetes the percentage mortality from arteriosclerosis is one-third greater than for the population as a whole, if we take Massachusetts for a criterion, because in this state it is responsible for 37 per cent of the total mortality.

Three years ago in Cleveland the relation of arteriosclerosis to diabetes was discussed<sup>1</sup> In the intervening

\*Read at the Minneapolis Meeting of the American College of Physicians, February 11, 1930

period new evidence in my own series of diabetic cases has been accumulating, and reference will be made to some of the statistical, clinical, X-ray, pathological and chemical findings

The scope of the investigation of the clinical material includes all true diabetic cases seen by me between 1894 and 1930 and of these 97 per cent have been traced. The causes of death have been verified by personal notes received from the family physician in most of those instances in which our information came from a death certificate Had it not been for aid received from the Metropolitan Life Insurance Company through its Medical Director Dr Augustus S. Knight, I could have hardly assembled the data, much less tabulated it The tabulation has been under the supervision of Dr Louis I. Dublin and under the immediate charge

TABLE I PERCENTAGES OF DEATHS OF DIABETICS DUE TO ARTERIOSCLEROSIS AND TO DIABETIC COMA IN EACH OF THE IMPORTANT ERAS OF TREATMENT.

	Total Deaths	Deaths from arterio-sclerosis, Percent	Deaths from coma, Percent	Average duration of diabetes
Naunyn—1894-June 1914	342	15	61	47
Allen—June 1914 to August 1922	805	26	42	5.4
Banting—August 1922 to 1929,* Total	979	44	17	8.1
August 1922-Dec 31, 1925	505	40	22	7.6
January 1, 1926-1929*	474	48	11	8.7

\*Includes deaths up to anniversary of treatment in 1929 except among cases treated prior to August 7, 1922, who are traced to August 7, 1929

of Mr Herbert Marks For purposes of tabulation and to guard the identity of the patients case numbers and not names of patients have been sent on transcribed cards to the office of the Metropolitan Life Insurance Co

#### *Rise in Arteriosclerosis Explained*

The most important reason for the rise in arteriosclerosis as the cause of death is the fall in the mortality from coma This has dropped from 61 per cent in the Naunyn Era to 11 per cent in the 781 cases who had died the last 4 years Even youth escapes coma today and of our 10 fatalities among 412 children during the last 19 months only five were due to coma A second reason for the increased prevalence of arteriosclerosis is the greater length of life of the diabetic Although exceptionally he may not be born in the arteriosclerotic zone, as two-thirds are, he is now living into it My average fatal case now has survived diabetes 87 years and for the fourth and fifth decades of onset the duration is 127 and 111 years respectively These two reasons, the reduction of coma mortality and the prolongation of duration of the diabetic's life, have advanced the average age at death so much that about 1 year each year for the last 16 years has been added until it is nearing 60 years in contrast to 44 years in the Naunyn Era For my 34 fatal diabetics at the New England Deaconess Hospital last year it was 63.5 years as contrasted with the average age at death for all patients in the Deaconess proper which was 54 years and in the Palmer Memorial branch of the Deaconess, a hospital largely for chronic diseases, which was 59 years The diabetic is now dying old and this

complicates the arteriosclerotic problem How old the average diabetic is who dies is best realized if the average age at death of diabetics is compared with the average age of death for the entire population in the registration area for the United States In 1920 this age was 41.9 years

*Localization of Arteriosclerosis* The localization of the arteriosclerosis has been studied for all fatal cases The heart was the most frequent site, 19.1 per cent of the total mortality, next the legs 13.2 per cent as evidenced by gangrene, far less the brain, 7.2 per cent, and least of all the kidneys, 4.7 per cent Sex made no essential difference in the distribution of the arteriosclerosis, indeed in females it was but slightly less frequent in the heart, 17.4 per cent, but it was considerably more common in the brain 8.8 per cent

If one compares the localization of the arteriosclerosis for the different epochs, the Naunyn, the Allen, and the Banting, it will be found that the percentage of deaths due to arteriosclerosis in the brain remains constant while that of the heart and peripheral arteries increases at the expense of the kidneys, the importance of which possibly may have been over rated in the Naunyn Era

*Age of Onset of Diabetes in Relation to Arteriosclerosis* The age of onset of the diabetes is important in any study of arteriosclerosis, because it can be assumed that if any of us die of old age arteriosclerosis will be the cause Table 4, which brings out the relation of arteriosclerosis to the decade of onset, contains 8 cases who died of this complication although the

TABLE 2. INCIDENCE OF ARTERIOSCLEROSIS AS A PRIMARY CAUSE OF DEATH AMONG 979 DECEASED DIABETIC EX-PATIENTS BY TYPE OF ARTERIOSCLEROSIS, BY SEX AND BY AGE AT ONSET AUGUST 7, 1922-1929\*.

PERCENT OF ALL DEATHS AT SPECIFIED AGES									
DEATHS									
Age at death	Total	Arterio-sclerosis All types	Apoplexy	Arterio-sclerosis and gangrene	Cardiac and angina pectoris	Nephritis	Arterio-sclerosis	Apoplexy	Nephritis
Both Sexes									
All ages	979	432	70	129	187	46	441	72	191
Under 30	96	2	—	—	2	—	21	—	—
30-39	53	5	—	—	4	2	113	—	21*
40-49	78	16	2	4	8	2	205	26	75*
50-59	248	107	17	23	53	14	431	69	103
60-69	349	202	27	71	86	17	579	80	214
70-79	134	84	21	26	28	9	627	157	246
80-89	21	15	2	5	6	2	714	95	209
									286
Males									
All ages	514	224	29	69	106	20	436	56	206
Under 30	60	1	—	—	1	—	16	—	16*
30-39	27	5	—	—	3	2	185	—	111*
40-49	43	10	1	2	6	1	233	23*	140*
50-59	127	60	10	13	32	6	472	79	252
60-69	178	98	12	39	41	6	551	67	230
70-79	67	43	5	14	20	4	642	75	299
80-89	12	7	1	2	3	1	583	83*	250*
									83*
Females									
All ages	465	208	41	60	81	26	447	88	174
Under 30	36	1	—	—	1	—	28	—	28*
30-39	25	1	—	—	1	—	40	—	40*
40-49	36	6	1	2	2	1	167	28*	56*
50-59	121	47	7	11	21	8	388	58	174
60-69	171	104	16	32	45	11	608	94	163
70-79	67	41	16	12	8	5	612	239	119
80-89	9	5	1	3	3	1	889	111*	333*

\*Because of the small number of deaths from arteriosclerosis, percentage distribution not significant

\*Includes deaths up to the anniversary of treatment in 1929 except among cases treated prior to August 7 1922 who are traced to August 7, 1923

who are traced

TABLE 3 LOCALIZATION OF TERMINAL LESION IN DEATHS OF DIABETICS DUE TO ARTERIOSCLEROSIS IN EACH OF THE IMPORTANT ERAS OF TREATMENT

Site of Terminal Lesion	Percent of All Deaths Due to Arteriosclerosis		
	Naunyn Period	Allen Period	Banting Period
Brain	17	18	16
Kidneys	23	14	11
Heart	37	41	43
Peripheral arteries	23	27	30

onset of their disease was in the first three decades. These few cases would not appear significant when we are dealing with so many, were it not that 6 of them occurred in the last 4 years when young diabetics are living longer. Reference will be made to them later. Similarly, as showing the change in the direction of the wind, in the fourth decade of onset the arteriosclerosis has risen markedly and in fact has doubled between the early and late periods of the Banting Era. Thus, of 46 deaths in those whose disease began between 30 and 40 years arteriosclerosis was re-

sponsible for 41.3 per cent. Such a percentage would not be expected for the population as a whole. Of course these data are misleading to this extent in that they are based upon age at onset and they become less striking when we realize upon the average the patients lived 12.7 years after onset before death came.

*Arteriosclerosis Increases with Duration of Diabetes.* With increasing duration of the diabetes arteriosclerosis rapidly rises as a causative factor of death. If the duration is less than 5 years, arteriosclerosis leads to 30 per

TABLE 4 INCIDENCE OF ARTERIOSCLEROSIS AS A PRIMARY CAUSE OF DEATH AMONG 979 DECEASED DIABETIC EX-PATIENTS BY AGE PERIODS AT ONSET

Age at Onset	Whole Period — August 7, 1922-1929			Aug 7, 1922—Dec 31, 1925			1926-1927		
	Total deaths	Deaths from arterio-sclerosis	Percent of total deaths	Total deaths	Deaths from arterio-sclerosis	Percent of total deaths	Total deaths	Deaths from arterio-sclerosis	Percent of total deaths
All ages	979	432	44.1	505	203	40.2	474	229	48.3
0-9	19	1	5.3	14	1	7.1	5	—	—
10-19	46	2	4.3	30	—	—	16	2	12.5
20-29	60	5	8.3	44	1	2.3	16	4	25.0
30-39	94	28	29.8	48	9	18.8	46	19	41.3
40-49	236	110	46.6	118	57	48.3	118	53	44.9
50-59	295	165	55.9	139	74	53.2	156	91	58.3
60-69	180	94	52.2	89	49	55.1	91	45	49.5
70-79	47	25	53.2	22	11	50.0	25	14	56.0
80-89	2	2	100.0	1	1	100.0	1	1	100.0

\*Includes death up to anniversary of treatment in 1929 except among cases treated prior to August 7, 1922, who are traced to August 7, 1929.

Site of Terminal Lesion                      Brain C                      71



cent of the deaths, if 5-9 years to 44 per cent, if 10-14 years to 63 per cent, if 15-19 years to 60 per cent, and if 30 years or over to 68 per cent If diabetes originates in an individual between 50 and 59 years old his chances of dying of arteriosclerosis are 2 to 1 if he lives 15 years and still higher if he lives longer. The effect of growing duration of the diabetes upon the

arteriosclerosis is more apparent now than a few years ago.

*Arteriosclerosis Especially Frequent Among Jewish Diabetics.* The influence of race appears to have a definite effect upon arteriosclerosis mortality in diabetes Thus it is decidedly more prone to be a factor in Jews. Of Jewish deaths 54.2 per cent were due to arteriosclerosis, in contrast to 43

TABLE 5A INCIDENCE OF ARTERIOSCLEROSIS AS A CAUSE OF DEATH AMONG 979 DECEASED DIABETIC EX-PATIENTS BY DURATION OF DIABETES IN SPECIFIED AGE PERIODS AT ONSET

PERCENT OF DEATHS DUE TO ARTERIOSCLEROSIS						
Duration of Diabetes (In Years)						
Age at Onset	Total	Less than 5	5-9	10-14	15-19	20 and over
All ages	44	30	44	62	60	68
0-9	5	6	—	—	—	—
10-19	4	3	—	—	100	—
20-29	8	—	20	33	—	33
30-39	30	9	6	27	54	81
40-49	47	22	50	52	57	65
50-59	56	37	54	80	67	78
60-69	52	52	47	65	67	—
70-79	53	50	60	67	—	—
80-89	100	100	—	—	—	—

\*Includes deaths up to anniversary of treatment in 1929 except among cases treated prior to August 7, 1922, who are traced to August 7, 1929

TABLE 5B PERCENTAGE OF DEATHS DUE TO ARTERIOSCLEROSIS AMONG DIABETICS ACCORDING TO DURATION OF THE DISEASES FROM ONSET TO DEATH.

Duration of Disease	Total Deaths	Arterio-sclerotic Deaths	Percent Arterio-sclerotic Deaths
Total	979	432	44.1
Less than 5 years	412	123	29.9
5-9 years	242	106	43.8
10-14 years	177	110	62.1
15-19 years	101	61	60.4
20 and over	47	32	68.1

\*Includes deaths up to anniversary of treatment in 1929 except among cases treated prior to August 7, 1922, who are traced to August 7, 1929

TABLE 6 INCIDENCE OF ARTERIOSCLEROSIS AS A CAUSE OF DEATH AMONG JEWISH DIABETICS COMPARED TO NON-JEWISH DIABETICS

	JEWS			NON JEWS		
	Total deaths	Arterio-sclerotic deaths	Percent arterio-sclerotic deaths	Total deaths	Arterio-sclerotic deaths	Percent arterio-sclerotic deaths
Both Sexes	96	52	54.2	883	380	43.0
Males	40	19	47.5	474	205	43.2
Females	56	33	58.9	409	175	42.8

\*Includes deaths up to anniversary of treatment in 1929 except among cases treated prior to August 7, 1922, who are traced to August 7, 1929

per cent for non-Jews. The percentage of arteriosclerotic deaths in Jewish women was 58.9 per cent as contrasted with 42.8 per cent for non-Jewish women

*Arteriosclerosis in the Youthful Diabetic* My concern for the high mortality from arteriosclerosis in my diabetics might appear unwarranted did not I know that this complication is beginning to make itself felt among the group who die under 40, even under 30 years of age. Thus Elizabeth J., Case No. 4079, in the early twenties while driving with her fiancé had a pain in her heart and died in 5 minutes. Premonitory symptoms had been present for a week. Cases 1794 and 2703, when but 33 and 30 years of age respectively, died of angina and coronary thrombosis, as did a case of Anderson<sup>2</sup> at 33, the lesions being demonstrated by post mortems. In fact among the 212 instances of definite angina pectoris in our series my associate Dr. Root will shortly report, there were 7 cases with onset of angina under the age of 40 years and in the decade 40 to 50 years there were 31 patients. Furthermore, one-sixth of all diabetic deaths in patients who contracted the disease un-

der 40 years of age in my group and one-third of all under 50 years of age were due to arteriosclerosis in one or another of its various forms. In Dr. Root's total series of angina cases there was but one case in 12 in which the onset of angina pectoris preceded that of the onset of diabetes. And it is of significance for the etiological relation existing between diabetes and angina pectoris to add that of 209 cases of angina there were as many as 88 females or 42 per cent in contrast to the usually high percentage of males, 75 per cent, in 827 cases of angina pectoris reported by Brooks, Kahn and Borsky, Levine, Kahn and Schmidt.

*Even Children Have Arteriosclerosis* As yet one can hardly say they die of it, because so few die. Thus for the last 19 months our mortality among diabetics who have developed diabetes in childhood (under 15 years) has been 1.5 per cent annually. But of these 10 deaths half have been due to coma, the balance being ascribed to nephritis or to sudden, presumably cardiac, deaths, subsequent to infections. Therefore, we are forced to look for evidence of arteriosclerosis among the living children and we have

found it by X-ray through the help of Dr L. B. Morrison and Dr. Bogan

Ten of our children show calcification of the arteries of the legs by X-ray, Case Nos 1616, 2007, 2105, 2353, 2432, 2617, 2757, 2870, 3620, 6416. Nine of these children are still living, one, Case No 2432, has died having had diabetes 16 5 years and his death certificate read chronic nephritis, arteriosclerosis, chronic colitis and morphinism—and I understand sometime previously he had had gangrene of one toe. The point has been raised that occasionally calcified arteries can be seen in non-diabetic children. This is undoubtedly true and incidentally I would ask if anyone here has a reference in the literature to such cases if he would be kind enough to give it to me. We have controls for our 9 cases of arteriosclerosis in children and these are none other than our diabetic children themselves. Thus in our group of diabetic children to date Drs Morrison and Bogan have never found arteriosclerosis unless the diabetes has existed at least 5 years and the average duration of the diabetes at which it has been found has been nearer 10 than 5 years. We shall watch with much interest the future of the remaining 8 children whom we know have arteriosclerosis.

*Cholesterol.* The importance of cholesterol in diabetes and still more in the etiology of arteriosclerosis in diabetes is still unsettled. Each new series of statistics published advances our knowledge and I look upon the same as new links in the chain of evidence rather than as conclusions. The papers by Hunt and by White and Hunt from our clinic bring out very clearly

that hypercholesteremia is amenable to treatment and therefore only of prognostic value in that it shows that treatment is faulty. Dr Geyelin will go a step further I am sure in an article which will shortly appear. Time is necessary to assess the part played by cholesterol in diabetes and the value of the work of White and Hunt lies in the fact that it gives the data for 100 of our children over a period of 4 years. Among these 100 children the latest analysis for cholesterol showed it to be normal in 80 and to be falling in six more. In four of the nine cases of sclerosis in children it was high, it was high in two of the four cases with tuberculosis, in the patient with a cataract, and of course high during coma and xanthoma. Adolescent children are apt to have high cholesterol values which eventually decrease.

Blood cholesterol values are not found to be high in our adult cases who show arteriosclerosis. The group with the lowest average cholesterol is the group with the greatest arteriosclerosis. Neither can the cholesterol values in our series be definitely correlated with any impending or existing arteriosclerotic process.

The aortae of 100 cases, diabetic and non-diabetic at the New England Deaconess Hospital, have been chemically examined for cholesterol, total lipid and iodine numbers. This work is not yet quite ready for publication.

Definite data upon the diets of the diabetic children and also of adults who show or do not show arteriosclerosis I cannot give. One will look far to find a living diabetic today who has had diabetes for 10 years and is not

taking carbohydrate 100 grams or more. Nearly all my children and practically all my adults take at least that quantity. As we all strenuously urge our diabetics not to overeat and thus get fat, and have given a higher amount of carbohydrate, it has necessarily reduced the content of fat. The future will show the results. So far as I can see our only test for the efficacy of this change will be the advancing average at death of all diabetics. In my group I have already said it has advanced about 16 years in the last 16 years. How long will this go on? It has just occurred to me that the doctors in the United States will serve as a valuable control series for our diabetics. The diabetics, it is true, outnumber them 3 or more to 1, but it should be possible to gather reliable statistics for each group.

*Eggs* I do not give my diabetics over 50 years of age more than one egg a day. One diabetic Case No. 3017 with marked arteriosclerosis reduced his consumption of eggs from two to four daily to none at all, and his cholesterol fell to normal. But like so many experiments this was complicated by the rearrangement of his diet made possible by the use of insulin. In a limited group of cases diets rich in eggs did not lead to high cholesterol values. Today we know that restriction in calories helps to reduce cholesterol just as does restriction of fat.

*The Retinal Vessels in Diabetes* The condition of the vessels in the eyes of diabetics is being studied by Dr. J. H. Waite and Dr. W. P. Beetham at the Deaconess Hospital. Thus far they have examined 306 patients and

their tentative conclusion is that diabetes does promote sclerosis in the ocular vessels. Arteriosclerosis is practically absent in patients under 30 years of age, but present in 95 per cent of all diabetic patients over 50 years of age.

Analysis by duration of diabetes shows small increments in prevalence and degree of sclerosis. For diabetics over 30 years under 1 year duration and counting all four degrees of retinal sclerosis the incidence is 75 per cent, rising to 86 per cent for those over 10 years duration. If only grades 2 and 3 of sclerosis are considered and the age limit raised to 40 years, the percentage for the cases under 1 year's duration is 40, for 1-10 years' duration is 44 and for 10-20 years' duration is 52 years.

*Roentgen Ray Allusion* has already been made to the incidence of arteriosclerosis in children as demonstrated by examination with the X-ray. Eventually Drs. Morrison and Bogan<sup>6</sup> will report upon a consecutive series of studies which they have made of 1000 of our cases and through their courtesy I can now refer to 298 unpublished instances in which they have looked for calcification of the vessels of the legs. In brief arteriosclerosis is demonstrable in the legs of 50 per cent of these diabetics whose diabetes is under 5 years' duration, and 52 per cent when the duration is between 5-9 years, in 84 per cent when the duration is 10-14 years and in 93 per cent if the duration is above 15 years.

*Pathology* The autopsy table shows end results. A monograph upon the Pathology of Diabetes by Shields Warren is now in press and I antici-

TABLE 7. INCIDENCE OF CALCIFICATION OF THE VESSELS OF THE LEGS IN DIABETICS MELLITUS AS DEMONSTRATED BY ROENTGEN RAY

Duration of Diabetes Years		Decade of Onset of Diabetes								Tot
		0-9	10-19	20-29	30-39	40-49	50-59	60-69	70-79	
0-4	Cases	8	14	8	11	11	33	13	5	103
	Calc. percent	0	0	13	36	27	82	100	80	50
5-9	Cases	22	24	13	12	14	23	7	0	115
	Calc percent	23	25	38	50	71	91	100	0	52
10-14	Cases	0	3	3	11	13	8	0	0	38
	Calc percent	0	33	33	82	100	100	0	0	84
15-19	Cases	0	0	0	7	7	9	0	0	23
	Calc percent	0	0	0	100	86	100	0	0	96
20+	Cases	0	0	2	8	6	3	0	0	19
	Calc percent	0	0	50	88	100	100	0	0	90
Totals	Cases	30	41	26	49	51	76	20	5	298
	Calc percent	16	17	31	67	75	89	100	80	61

pate with satisfaction the pleasure you will have in its perusal It is based upon 300 diabetic autopsies, chiefly performed in Boston, but the balance under the supervision of his friends who are some of our most distinguished American pathologists To such a diabetic collection of autopsies it is the privilege and duty of each physician here to make a contribution Owing to the kindness of Dr Warren I can refer to some of his findings.

All of us work hard to improve the status of our diabetics, but I conceive it a reproach upon us all that Dr. Warren is obliged to say that in his series of 300 diabetic autopsies there has

been no case with diabetes of 5 years' duration which did not present arterio-sclerosis This cannot be explained upon the ground of the age of the patient, because 80 of the 300 or 264 autopsies were in individuals below the age of 40 years I am sure the time is not far distant when the medical profession can improve this record and I urge all to watch for an autopsy upon a diabetic whose diabetes is more than 5 years' duration and yet shows no arteriosclerosis and to be the first to put such an one on record for the benefit of us all.

Arteriosclerosis was the cause of death, as shown by autopsy, of 24 per

cent of the deaths in Warren's 300 cases, despite the fact that 80 of the cases were, as said above, under 40 years of age. Of the 23 cases of diabetes of 15 years' duration or over there were 13 or 56.5 per cent who died from arteriosclerosis. Nine of these 23 cases of 15 or more years' duration had gangrene.

The incidence of arteriosclerosis as well as its incidence as a cause of death is recorded in Table 8.

The site of arteriosclerosis in the body which was responsible for the 72 arteriosclerotic deaths is shown in Tables 10 and 11. Arteriosclerosis of the heart was responsible for 43 per cent of these deaths, of the legs for 37 per cent, of the brain, for 11 per cent of the kidneys for 6 per cent and the arteriosclerosis was generalized in 2.8 per cent. Among the patients who had had diabetes 15 or more years and died of arteriosclerosis the heart

TABLE 8 INCIDENCE OF ARTERIOSCLEROSIS BY DECADES AT AUTOPSY

Age at death in years	Total Cases	Arterio-sclerosis present	Deaths due to arterio-sclerosis	Total incidence of arterio-sclerosis	No arterio-sclerosis
0-10	9	0	0	0	9
11-20	23	7	0	7	16
21-30	19	10	0	10	9
31-40	21	18	1	19	2
41-50	36	29	6	35	1
51-60	66	48	17	65	1
61-70	65	30	35	65	0
71-80	19	7	12	19	0
81+	2	1	1	2	0
?	4	3	0	3	1
Total	264	153	72	225	39

The condition of the aorta was recorded in 226 instances and in but 29 was it free from arteriosclerosis. In 101 instances the arteriosclerosis was of a severe type in contrast to the sclerosis in the kidneys which was severe but 11 times.

was the cause of death in 69 per cent, the extremities in 23 per cent, and the brain in 8 per cent. In 263 diabetic autopsies there were 54 with infarctions of the heart (Table 12) which is from 3 to 10 times the percentage in large general series of autopsies.

TABLE 9 INCIDENCE OF ARTERIOSCLEROSIS IN 226 FATAL DIABETIC CASES

Arteriosclerosis of	Slight	Moderate	Severe
Aorta	35	61	101
Kidney	49	47	11

The association of coronary sclerosis with gangrene is very striking. Fourteen cases showed both gangrene and infarcts of the heart, healed, fresh, or both. Thus 25.5% of the 55 cases of gangrene occurred in conjunction with infarcts of the heart.

TABLE 10 ARTERIOSCLEROTIC DEATHS  
AMONG 300 DIABETIC AUTOPSIES

Arteriosclerosis of		
vessels of	Number	%
Heart	31	43 1
Extremities	27	37 5
Brain	8	11 0
Kidneys	4	5 6
Generalized	2	2 8
	—	—
Total	72	100 0

TABLE 11 ARTERIOSCLEROSIS AMONG 23  
DIABETIC AUTOPSIES

Duration of Diabetes 15 Years or Over

Arteriosclerosis of		
vessels of	Number	%
Heart	9	69 2
Extremities	3	23 1
Brain	1	7 7
Kidneys	0	0 0
Generalized	0	0 0
	—	—
Total	13	100 0

TABLE 12 INCIDENCE OF INFARCTS OF HEART AND CORONARY THROMBOSIS IN  
263 DIABETIC AUTOPSIES

	Fresh	Healed	Fresh and Healed	Total	Coronary thrombosis without infarction
No Cases	9	18	7	54	2
Av age in years	59	63 7	61 1		66
Av duration in years	11	12 5	12 4		?

The predominance of arteriosclerosis in the arteries of the heart and legs of diabetics is significant. In the vessels here in question the muscularis overshadows the elastic tissue. Incidentally the rarity of endocarditis is striking and so too the prevalence of glycogen in the muscle fibres about the margins of infarcted areas. The low percentage of arteriosclerotic deaths due to the arteries in the brain may be associated with the comparatively few cases of high blood pressure. But I should add that Dr. Root has called my attention to the growing number of

cases who gradually are developing cerebral thrombosis.

Is the high frequency of arteriosclerotic deaths from lesions of the legs to be ascribed to the character of their arteries and the extent of the sclerosis or are these deaths really to be ascribed to trauma and infection? This is a query also raised by Root. No doubt trauma and infection are potent precipitating factors, but Dr. Warren feels from his pathological studies, based upon autopsies and amputated legs of diabetics, that the diabetic sclerosis is distinctive. He elaborates and gives reasons for this in his forthcoming monograph. Every case, however, we can rescue from a death due to gangrene will lessen the importance of the distinction and I do

not forget that formerly one of every group of eight diabetics and even in the last four years one in eleven whom I have seen died from this cause.

*The Future of the Diabetic* It is only a little over a generation ago that one-half of the diabetics succumbed to tuberculosis and I suspect that physicians then considered this end inevitable, but now tuberculosis is no more frequent among diabetics than in the population at large and in 32 years in my group of more than 600 children only 3 of the children have died of it, but 3 are alive with pulmonary tuber-

culosis, and 7 others have tuberculous lesions in other parts of the body. Diabetic coma replaced tuberculosis and in the first half of this present generation 60 per cent of my patients died of it. When in 1922 I reported that in the preceding 7 years my coma mortality had fallen to 40 per cent and that I believed coma preventable, the statement was received with scorn, yet by the end of 1926 you will remember the percentage had dropped to 20 per cent and now for Massachusetts, and incidentally as well for my own series of cases, to 11 per cent. Arteriosclerosis now rules the scene and you and I have seen it grow from 15 per cent to 50 per cent. Must we feel as hopeless about arteriosclerosis today as were some physicians a generation ago about tuberculosis and other physicians half a generation ago about coma? I believe not. It is true we cannot conquer old age, but we can conquer *premature* old age and you and I know that much of the damage which arteriosclerosis produces is preventable. We can fight gangrene this year as we fought coma last year and with success. I am beginning to be ashamed to have one of my patients die of gangrene as I was eight years ago to have one die of coma. I feel that if I make it a rule at a diabetic's first visit to look at his feet before I look at his face, ipso facto, his chances later of dying of gangrene will be almost negligible. I do more. I look at the feet at each visit and tell the patient that I do so, so as to insure him against gangrene. Of course, I realize there are poor risks in all kinds of insurance.

And can you prevent or at least postpone arteriosclerosis of the heart? I

also believe you can, because I find that as the years go by each series of the diets of my patients is more and more closely approximating the diets of those in health. At one time my diabetic patients received 25 grams of carbohydrate and the poor cases who escaped coma fell a prey to arteriosclerosis; then the carbohydrate in the diet began to rise to 44 grams, to 63 grams, to 71 grams, to 96 grams and recently I found that comparable diabetics who were discharged without insulin in 1922 with carbohydrate 77 grams now leave the hospital with 147 grams. In fact a survey of all the diabetics on one chance day early this year undergoing treatment at the Deaconess showed they were receiving 125 grams carbohydrate, 63 grams protein and 92 grams fat with glycosuria and glycemia controlled in large degree. If our diets approach the normal, while diabetic symptoms are held in abeyance by insulin and exercise, our diabetics should live about as long as the average individual.

Diabetic children are precocious in height, weight and mentality, the offspring of diabetic mothers tend to be large, our cardiac specialists give glucose for angina pectoris, our surgeons depend upon glucose, when the blood sugar is low, diabetics, and this applies to non-diabetics too, are mentally sluggish and faint. Our blood sugar may rise normally after meals to an extent we should term a diabetic blood sugar if taken before a meal. I wonder if a little hyperglycemia now and then may not be a good thing. Clemenceau with diabetes won the war. Would he have been as vigorous at 77 and as successful without it?



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# Unrecognized Hyperthyroidism Masked as Heart Disease\*

SAMUEL A. LEVINE, M D , *Boston, Mass*

THE subject of this discussion concerns itself with a group of patients who suffered from one or another form of heart disease not unlike those customarily seen in any general practice but in whom a previously unrecognized element of hyperthyroidism proved to be a most important factor. The great importance of this undetected burden to the circulation will become clear when the therapeutic results obtained are taken up. At the outset it must be understood that the cases which form the subject of this problem are not the "ordinary" cases of exophthalmic goitre or toxic adenoma. They are not the ordinary ones in the sense that they show no exophthalmos or detectable thyroid tumor, the two presenting features of Graves' disease. They are not the ordinary ones in the sense that they are not recognized as such even at the present time by many of the most competent internists, surgeons, or even heart specialists. They come to the physician complaining of various heart symptoms, may be referred to a heart specialist and be treated for heart disease and therefore hardly ever

get to a surgeon because there is no apparent surgical problem involved. They suffer increasing circulatory disability and may eventually die of heart failure and yet had the true nature of the disease been recognized, they might have been cured or at least the condition might have been greatly helped, their suffering diminished and their lives prolonged. It must therefore be quite clear that these cases are to be looked for anew, with somewhat different criteria than those to which we have been accustomed and are not to be confused with the ordinary cases of hyperthyroidism which now show cardiac complications.

Great studies have been made in our knowledge concerning the diagnosis and treatment of thyroid disease during the past ten or fifteen years. With the clinical introduction of basal metabolism determinations, the splendid improvement in the surgical technique and the recent introduction of the preoperative use of iodine, the surgical mortality of operations on the thyroid gland has fallen to a very low level. There is no longer the same fear that attended such operations not so many years ago. It is pleasing to note that this country has had no insignificant part in the above development. We have also witnessed very

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dramatic improvement in the state of the circulation in those patients suffering from hyperthyroidism in whom previous to operation, there was gross evidence of cardiac failure. It is with the aim that similar beneficial results might be rendered to heart cases that are at present overlooked that this discussion is directed.

When there is exophthalmos or a definite enlargement of the thyroid gland our attention is immediately called to the diagnosis of hyperthyroidism, no matter what the cardiac signs or symptoms may be. Under such circumstances the diagnosis at least is simple. Proper basal metabolism determinations are made and when correctly interpreted the decision whether the gland is hyperactive or not may be made. But if these two cardinal features are absent and the patient presents himself with symptoms and signs that are at first glance those customarily seen in ordinary heart failure, the possibility of an underlying hyperthyroidism is lost sight of and the routine administration of digitalis, rest, and the like is instituted. The patient then does not improve but instead slowly grows worse and may eventually die. It is striking, however, that when such patients reach the stage of advanced cardiac failure, they may continue to live months or even years longer than one would have prognosticated. They seem to have an unusual tenacity for life. If any large group of heart patients is investigated in the light of the following discussion, it is very likely that some will be found to be suffering with a certain degree of hyperthyroidism that had previously been unrecognized.

The difficulties in diagnosis become greater still in certain instances, because it is now quite well known that hyperthyroidism may be present in patients suffering already from some other form of heart disease such as mitral stenosis, hypertension, or angina pectoris. It then seems so simple to explain all the symptoms on the basis of the obvious diagnosis, that the additional burden from hyperthyroidism is overlooked. Because the physical findings in the heart in mitral stenosis resemble very closely those found in hyperthyroidism, these two conditions particularly are frequently confused and the possibility of the presence of both simultaneously must be kept in mind.

What are the means employed to diagnose these obscure cases? The most helpful is the general appearance of the patient. The skin of the face is warm, moist, hyperaemic and slightly pigmented, producing a salmon-colored appearance. This often serves as the first clue to direct attention to the thyroid gland. Certain points in the history of the patients are also helpful. They are apt to prefer cold to warm weather, using less than the ordinary protection for their bodies in winter. On direct questioning it may be found that although they do not complain of any gastro-intestinal trouble, they have had short periods of unexplained frequency in bowel movement and attacks of vomiting. Weakness, although generally present is so common in ordinary heart disease that it is not sufficiently distinctive to make one think of hyperthyroidism. The same is true of loss of body weight. Ordinary cardiacs may lose considerable weight

during the course of years, but when hyperthyroidism is present, the loss may be very great and occurs in a shorter time. This loss can occur despite an excellent appetite, although not all the patients, however, have a good appetite. They are apt to feel nervous and in some cases this is displayed by rather alert and quick movements, not customarily seen in patients, otherwise sick with heart failure. In other words the ordinary cardiac with congestive heart failure or with angina pectoris is not generally seen to be moving around unnecessarily in bed whereas these patients may appear hyperactive. Although there is no exophthalmos some may show a peculiar stare to the eyes. It may be ascertained from the past history that they had slight glycosuria off and on and may have been treated for mild diabetes. A tremor of the fingers is generally but not invariably present and the thyroid gland is either not felt at all or is only questionably enlarged. Unexplained perspiration is a striking phenomenon in some cases and many have premature grayness of the hair.

Inasmuch as these patients present themselves primarily with cardiac complaints the heart findings are of extreme importance, especially those that are peculiar to hyperthyroidism. The most characteristic of these is periods of transient auricular fibrillation. There is no other condition in which this occurs so frequently and it would be well to suspect hyperthyroidism in any patient who shows this disturbance no matter what other disease may already exist. The quality of the heart sounds is peculiarly hyperactive and loud. The first heart sound has the same intensity

that is seen in well compensated mitral stenosis. Generally with this there is a slight to moderately loud systolic murmur heard at the apex or at the base of the heart and frequently an accompanying vibration or thrill. When the thrill can be timed properly it will be found to occur with systole. Often accurate timing of the thrill is difficult or impossible because of the rapidity of the heart. Under such circumstances the observer is prone to consider it as presystolic because he is prejudging the case as one of mitral stenosis. For similar reasons and because the first heart sound is snapping, the murmur that accompanies it may wrongly be considered as presystolic. Such mistakes have actually been made by most competent observers. I well remember making that same error many years ago in a case that showed no evidence of mitral stenosis at autopsy, but instead an extremely toxic hyperthyroidism. It is easy to see how these conditions can be confused, because they both may have heart failure, rapid heart, auricular fibrillation, a snapping first sound, a thrill at the apex and a systolic murmur. The one critical difference on physical examination is that in hyperthyroidism there is no murmur or thrill in diastole. However, both conditions may exist simultaneously and the diagnosis will then rest on other evidence.

There are further characteristics of the heart that should make one suspect hyperthyroidism. One of these is a failure to obtain slowing of the ventricular rate in a case of auricular fibrillation after proper digitalis administrations. In the ordinary case, unless there is fever, the heart rate

slows to between 60 and 80 on full doses of digitalis. When hyperthyroidism is present, although such slowing occasionally occurs, more commonly it is impossible to obtain a rate under one hundred. That single feature has on occasions been the first intimation that the metabolism would be found elevated. A further finding is the persistence of a regular heart rate of over 90 at rest in bed, in the absence of fever. Most ordinary heart patients with a regular rhythm will show a rate of 80 or under after a few day's observation in bed, even if there is decompensation. Of course many functional heart patients will have a slight tachycardia even in bed, but then if the heart rate is counted while the patient is asleep, it will be found to slow, whereas a rapid tachycardia is apt to persist in hyperthyroidism. It must not be forgotten, however, that active hyperthyroidism may be present with a slow ventricular rate. I have seen several such cases in which the rate was only 70 and one in which it was only 40. In addition to these heart findings the blood pressure readings are of some importance. Although hyperthyroidism itself does not produce any marked elevation in the systolic pressure, the pulse pressure is generally increased and it may be associated with a concomitant true hypertension. The foregoing features of the circulation serve as important aids in the clinical diagnosis of unrecognized cases of hyperthyroidism.

After a suspicion is aroused concerning the possibility of an unrecognized hyperthyroidism by one or more of the above criteria, a careful basal metabolism determination must be

made. If this is within normal limits the diagnosis can be dismissed. It is surprising, however, how often it will be found to be elevated in such a group of heart patients. The elevation in the metabolic rate will then need to be confirmed by repeated determinations. If it is persistently elevated one is faced with the question as to how much of the increase might be accounted for by decompensation of the heart itself. Heart failure in some instances is supposed to cause an increase in the basal metabolic rate, but from the experiences with these cases, it would seem that any increase of 40% or more should properly be regarded as due to a hyperactive thyroid rather than to the cardiac failure unless dyspnea is very marked. In fact, rates that were about plus 30% were regarded as such and were proved to be due to the thyroid gland by subsequent microscopic examinations. In the past many have been too quick to ascribe the increase in the metabolism to the heart failure merely because there was no exophthalmos or thyroid enlargement. I am of the opinion that some heart patients who have no more than a plus 20% metabolism but who show the above clinical features have true hyperthyroidism. Metabolism determinations always need to be repeated in order that the element of nervousness, apprehension and the like may not influence the reading. After the customary care has been taken, it then needs to be interpreted in the light of the clinical findings.

When it is decided that the patient has hyperthyroidism he should be kept in bed and started on iodine therapy in one form or another. It

does not seem to matter whether it is given in the form of Lugol's solution, potassium iodide or sajodin. In practically all of the cases of this group, ten drops of Lugol's solution were given three times a day. The treatment is otherwise carried out just as in any heart patient. If auricular fibrillation is present, digitalis in full doses is given. It will be noted in many cases that the ventricular rate will fall on digitalis therapy if iodine is given, whereas before this digitalis failed to produce any appreciable slowing. In general if the rhythm of the heart is regular, digitalis is not given. Diuretics can be used if edema persists, although during the preoperative medical care a diuresis is likely to occur even without the use of diuretics. The diet should be liberal as many of these patients have lost a great deal of weight. Sedatives should be used if necessary to produce sleep. In other words all the measures employed in the treatment of cardiac disease are applicable in this group in addition to the use of iodine. Metabolism determinations should be repeated to note the fall that takes place about five to seven days after the iodine is started. The general plan is to have the operation performed after the metabolism has fallen and the general condition of the patient and the circulation have improved as much as possible. At times under medical treatment the improvement is so marked that both the patient and even the physician might become doubtful as to the advisability of an operation. It is best in most cases, however, to operate just at this time because the improvement is not apt to be permanent and a later time may not

be as favorable. In general the optimum time for the operation will be found about ten to fourteen days after treatment was started.

In most of the cases included in this study the operation consisted of a one stage subtotal thyroidectomy performed under general anaesthesia. The anaesthetic used was ether (by mouth or by rectum) or ethylene. The exact choice does not seem to be very important and will vary with the surgeon. It is extraordinary how well these patients tolerate even a one stage operation. The thyroid gland will almost always be found a good deal larger than would have been anticipated from physical examination. Occasionally it will be found to lie almost entirely beneath the manubrium or behind the trachea where it could not have been felt. In all of these cases the pathological examination of the tissue removed showed hyperplasia of the thyroid.

The aim in therapy is to reduce the metabolism to normal. Sometimes this would have been accomplished even before the operation. In such cases surgery helps to prevent a subsequent rise. More often a fall of 20% or more would be obtained on medical care and a further fall after the subtotal thyroidectomy. Usually the return to a normal metabolic level is obtained within one to two weeks following the operation, although occasionally the level continues to fall for several weeks. If the metabolism is still distinctly elevated a month or so after the operation it generally means that certain symptoms of thyrotoxicosis will continue and that enough thyroid tissue had not been removed. Such

cases although much improved, may continue to have auricular fibrillation and it is difficult or impossible to restore the heart to a normal level so long as the metabolism is elevated. A second operation may then be advisable. If the metabolism returns to normal, the auricular fibrillation in most cases will spontaneously change to a normal rhythm within one to several weeks, but if it should not, then quinidine sulphate should be tried and may regularize the heart. The relief to the heart that results from diminishing the metabolism of the body will show itself in most extraordinary improvement of the symptoms and signs of heart disease. Beside the effect on auricular fibrillation I have witnessed the cure of Adams-Stokes syncopal attacks, of insufferable anginal attacks and the complete and permanent disappearance of intractable general anasarca.

This discussion would surely be incomplete and lose much of its value without reference to specific experiences which illustrate the features taken up above. The results obtained in the following cases (only a few of a much larger group) speak for themselves and merely emphasize the great importance of detecting these unrecognized instances of thyrocardiacs, for in no other group of severe heart cases can such dramatic and beneficial cures or improvement be obtained.

*Case 1* F. E. J., a banker, aged 63, came to Boston to seek aid for insufferable anginal attacks. He had previously been treated by various physicians in Buffalo, but was growing steadily worse. He had to stop working because of the great frequency of the attacks of anginal pain. He was sent to me (July 13, 1928) by his son who is a physi-

cian, with the purpose of having some surgical procedure carried out, such as a cervical sympathectomy or an alcohol injection for the relief of pain. The attacks began five years before, but during the past six months attacks of severe pain would come without effort and would even awake him from sleep. The attacks were generally relieved promptly by nitroglycerine, but he had to take on the average about 40 pills a day. Lately there had been some dyspnea with the attacks and fear of death.

Past history and family history were irrelevant.

Physical examination showed very little of importance. The heart was slightly enlarged, there was a soft blowing systolic murmur, both at the apex and the base but no diastolic. The blood pressure was 146/84. The lungs and abdomen were negative and there was no pitting oedema. The peripheral arteries were not remarkable. The urine showed a slightest possible trace of albumin, a few hyaline casts and occasionally a trace of sugar. The phthalein test was 60%. The Wassermann and blood counts were normal.

He had been treated by the ordinary methods before coming to Boston without any relief and while his condition was being studied under what seemed ideal conditions, he was still having 40 attacks of angina a day (10 to 15 during the night). He was at first regarded as an ordinary case of angina pectoris, but because of a recent failure to obtain relief by surgical measures I was at a loss as to what to do. After about one week of observation I became impressed with certain minor features that pointed to a possible hyperthyroidism. He was hyperactive while in bed, his movements being quick and jerky. This is so unlike the ordinary angina patient who prefers to keep still for fear of bringing on an attack. There was a slight tremor of the fingers. The skin was rather warm, hyperemic and moist. There was no exophthalmos, however, and the thyroid gland could not be felt. The heart rate was regular and ranged between 88 and 100. It was then learned that he had lost 15 pounds in eight months, although he had a fairly good appetite.

A metabolism test was therefore done on July 16th and found to be plus 41%. On ten drops of Lugol's solution, three times a day, the readings fell so that on July 21st it was plus 26%, and on July 24th it was plus 4%. With this there occurred a most extraordinary improvement in the condition. The number of attacks fell to only 4 a day and there were none at night. In addition the patient volunteered the following remark "something has happened inside of me, for I have not felt this way in years." A few days later a subtotal thyroidectomy was performed and a small hyperplastic gland was found extending below the manubrium. After the operation the anginal attacks entirely disappeared. He returned to his home and then to work. He had no attacks at all for 6 weeks and since then during the past year he has felt well and would have to take a nitroglycerine pill about once a week when he might hurry in the street or try to climb a hill.

#### SUMMARY

The extraordinary results obtained in this case can not be ascribed to anything else but the treatment of the hyperthyroidism. Most of the improvement to be sure was obtained temporarily at least by the preoperative use of Lugol's solution. Here a man was restored to his normal health and relieved of the suffering that accompanies 40 attacks of angina a day.

*Case 2* R S, a 63 year old housewife, was first seen in November, 1925. It was known that for at least eight years she had had hypertension. For some years she noticed a choking sensation in the center of the chest upon walking. During the past year there were several major spells of acute pulmonary edema. During these attacks suddenly she would become desperately orthopneic, the chest would fill up with moist bubbling râles, and the whole thing would clear up in fifteen minutes after a hypodermic injection of morphine.

Examination November, 1925, showed systolic blood pressure 220 mm and diastolic 100 mm. The heart was moderately en-

larger, the aortic second sound was ringing, and there was a moderately loud systolic murmur over the precordium. After a month's period of rest in bed the condition improved, and she again became ambulatory.

During the following year, typical anginal attacks developed. These consisted of a squeezing pain in the sternum, with radiation to the left clavicle, ear and arm. These attacks were relieved promptly by nitroglycerine. In May 1928 she was again seen, but the clinical picture was entirely changed. She was now suffering from cough and dyspnea, in addition to the frequent attacks of angina pectoris. It was noted that the skin was moist, warm and hyperemic and a grossly irregular rate of fibrillation was found for the first time. There was no tremor, exophthalmos or thyroid enlargement. The diagnosis of hyperthyroidism was made, which was confirmed by finding the metabolism rate to be plus 74. This was repeated two days later and was found to be plus 50. This patient was suffering so obviously from hypertensive heart failure, auricular fibrillation and angina pectoris and had so little that is customarily regarded as indicating hyperthyroidism, that even after these two basal metabolism readings were made, several members of the visiting staff of the hospital refused to believe that she was suffering from hyperthyroidism.

On June 4, 1928, Lugol's solution was started and several days later the heart rate began to slow. Previously, full doses of digitalis had no effect on the rapid irregular rate. There followed striking clinical improvement. The metabolism fell to plus 35, the heart rate slowed to about 70, the anginal attacks disappeared almost entirely, and the patient felt quite comfortable.

Subtotal thyroidectomy was performed July 6 and microscopic examination of the gland showed mild hyperplasia and fibrosis. Sixteen days after the operation, examination of the heart showed that auricular fibrillation was still present. She was given 2 grams of quinidine three times a day, and in twelve hours the heart became regular. She became ambulatory and entirely free of the anginal attacks.



## SUMMARY

This case illustrates the remarkable improvement that occurred in a cardiac patient, by properly treating the latent hyperthyroidism. Apart from the improvement in the more ordinary features of circulatory insufficiency, the striking result here was the specific disappearance of the angina pectoris.

*Case 3* M D R, a man 52 years old, was first seen in consultation December 27, 1928. He was then complaining of attacks of pain in the right chest, of a mild nature, for the previous two months, but which become quite severe during the last few days. They came both while walking and at rest. During the last day he had several very severe attacks, lasting about one-half hour, during which the pain radiated down both arms to the wrists. During one of these attacks he vomited. He had slight dyspnea for several years, and in 1926 his blood pressure was known to be 120 mm systolic and 65 mm diastolic.

Past history and family history were not remarkable, except that during the past six years, there was a gradual loss of 35 pounds in weight.

On examination very little was made out except that the heart sounds were distant, that there was a slight apical systolic murmur. The urine was negative, and the blood Wassermann and blood counts were normal. The blood pressure was 95 mm. systolic, and 60 mm diastolic. Electrocardiograms were not remarkable. He was sent to the hospital where he remained almost four months. He was treated for angina pectoris, but he continued to have frequent attacks of pain even with careful rest in bed, which were always relieved by nitroglycerine. After he had been observed for four weeks, it occurred to me that the appearance of the patient's skin and face was suggestive of hyperthyroidism. He had no exophthalmos whatever, and the thyroid gland was not palpable. Despite the fact that his pulse rate was around 70, and frequently lower than this, several metabolism tests were done, which were found to be plus 33. During these determinations, the heart rate

was 66 and 68. It was felt that these readings together with the moist hyperemic skin, slight hyperactivity of his muscular movements, a definite tremor of the fingers and the insidious loss of weight, all pointed to an active, moderate hyperthyroidism.

The anginal attacks continued unchanged until he was started on Lugol's solution January 31, 1929. Shortly after this there was a marked improvement. The attacks of angina became less troublesome and more infrequent. The metabolism dropped to plus 11, and then on February 16, to plus 6. Because of the obscurity of the problem and the skepticism on the part of some members of the hospital staff concerning the diagnosis of hyperthyroidism, an operation was not performed. He was given therefore four X-ray treatments over the thyroid, but the metabolism was not brought to normal. In fact it rose to plus 36, with return of more frequent attacks of angina. During the X-ray treatment, the Lugol's solution had been omitted. Later it was resumed, and there followed a second improvement, so that the attacks of angina almost entirely disappeared.

Shortly after leaving the hospital, the anginal pains returned. Therefore he was sent into the surgical service for an operation. The surgeons were very timid about operating, but upon urgent request a subtotal thyroidectomy was performed on May 21, 1929. Pathological examination of the gland showed diffuse hyperplasia with involution. Since the operation he has had no pain whatever, he has felt a great deal better and is now ambulatory. The metabolism was plus 20 on May 28 and plus 8 on June 5, 1929.

## SUMMARY

This case, had a mild latent hyperthyroidism, which was aggravating an existing angina pectoris. Because of the lack of support and enthusiasm on the part of my colleagues, both medical and surgical, operation was delayed several months and attempts were made to obtain relief by the use of Lugol's solution alone, and later by

X-ray therapy Operation finally relieved him of anginal symptoms The diagnosis of hyperthyroidism was here first thought of because of the appearance of the patient's skin, despite the very slow pulse rate

*Case 4* J A T, an American executive, was first seen in consultation December 4, 1926 He complained of fatigue and palpitation For two months he had noticed palpitation of the heart, particularly with exertion There were no pains whatever Although previously in excellent health, he recently found himself becoming tired readily He lost twenty-five pounds of weight in four months, although during this time he had an excellent appetite There was more than the usual perspiration, and his voice had changed in character Seven weeks before, he had had an inexplicable attack of diarrhea lasting seven days He had become somewhat nervous There was slight dyspnea on walking For several years he noticed that he frequently felt warm, when other people felt cold The above history was obtained on direct questioning because the appearance of the patient suggested hyperthyroidism The outstanding complaints on the part of the patient, when not pressed with direct questions, were palpitation and fatigue Past history and family history were not remarkable

On examination, the character of the skin of the face and neck was very impressive It was warm, moist, hyperemic, slightly pigmented and produced a salmon-colored appearance There was no exophthalmos or thyroid enlargement The lungs and abdomen were negative, and there was no peripheral edema There was no appreciable tremor The blood pressure was 140 mm systolic and 80 mm diastolic The heart was not enlarged The action was grossly irregular with an apex rate of 122 The pulse rate was 108 The heart sounds were distinctly hyperactive There was a short thrill at the apex No murmurs were heard The urine was negative except for a rare hyaline cast and the slightest possible trace of sugar

A diagnosis of hyperthyroidism was made, and the patient was advised to enter the hos-

pital for surgical treatment To confirm this clinical impression a basal metabolism was done the following morning and found to be plus 35 This diagnosis came as such a surprise to the patient and to his family physician, that further opinions were desired His doctor was a scrupulously honest and able physician He knew, as he said later, that if he sent this patient to another heart specialist with the knowledge of the previous diagnosis, he would inevitably be biased in his judgment He, therefore, directed the patient to tell the second consultant nothing about his experience, nor to mention anything concerning the diagnosis of hyperthyroidism, or of having had a metabolism determination done At this second consultation, one of the best known heart specialists in this country made the diagnosis of so-called myocardial disease and auricular fibrillation, and advised the administration of quinidine Upon getting this report, the family physician directed the patient to see the consultant again, but at this time to tell about his first experience Then a second metabolism was done, which was found to be plus 40, and he agreed that the patient was suffering from thyroid heart disease and should have a thyroidectomy The above experience is gone into in detail, merely to emphasize the obscurity of the condition, and to show how easily the true nature of the disease can be overlooked, even by a highly trained expert

The patient spent the next three months hoping to gain improvement on medical treatment, but grew worse He finally entered the hospital March 26, 1927 He still showed auricular fibrillation, and the metabolism test was plus 38 Ten drops of Lugol's solution were given three times a day The metabolism fell to plus 23 on April 2nd, and then to plus 8 on April 6, 1927 The heart rate, which previously could not be slowed with large doses of digitalis, gradually came down to a rate of 70, while he was receiving a grain and a half of digitalis, twice a day A subtotal thyroidectomy was performed on April 7th, and he made an uneventful recovery About ten days after the operation, the heart spontaneously became regular During the past three years, the patient has been perfectly well, has re-

gained his weight and strength, and the heart has been normal in every way

### SUMMARY

This patient would be regarded generally as suffering from ordinary myocardial disease with auricular fibrillation. The features which led to the proper diagnosis were the appearance of the skin, the hyperactive quality of the heart sounds, the failure to obtain slowing of the fibrillating heart with digitalis and finally the metabolism determination.

*Case 5* L. R., aged 36, entered the hospital, December 8, 1928, complaining of sore throat and attacks of palpitation. For many years he had had many sore throats, and during the past several months had had three attacks of palpitation. A month ago, he had a sudden spell of palpitation, became dizzy and later fainted. His doctor treated him for heart disease with digitalis. About a week later, he had another attack, and this time his physician advised tonsillectomy, which was done December 4, 1928. The day after the operation, a third attack of palpitation occurred.

When he was first seen on the medical service, he was considered to have mitral stenosis of rheumatic origin, and paroxysmal rapid heart action of a type that had not been determined. He had a slight fever of 100 F. The heart seemed slightly enlarged; the action was regular, rate between 70 and 80. The first sound was much accentuated, and there was a rough systolic murmur over the precordium. It was thought by some of the service that a slight presystolic murmur could be heard after effort. The blood pressure was 138 mm systolic and 62 mm diastolic. There was no peripheral edema or other evidence of congestion.

When he was seen a few days later, the possibility of hyperthyroidism immediately came up because of the salmon color and hyperemic appearance of the face. The signs in the heart were typical of mitral stenosis except for the absence of any murmur in diastole. It was further elicited

that the patient had lost weight, although he ate fairly well, and that he perspired rather freely. It was predicted that if an attack of palpitation could be carefully observed, it would be found to be due to a transient auricular fibrillation. Electrocardiograms were subsequently obtained during one such spell, which confirmed this diagnosis. There was no exophthalmos, only a doubtful tremor and the thyroid gland was not palpable. The blood examination was negative, the urine showed an occasional trace of sugar up to 0.5%. The first metabolism reading on December 14, 1928, was plus 67%. Subsequent readings ranged around plus 40 to plus 70. The metabolism was markedly elevated despite the fact that the heart rate was generally around 70.

Although I was convinced of the accuracy of the diagnosis of hyperthyroidism, it was difficult to make either the other medical attendants or the surgeon who saw him in consultation, believe this. The elevated metabolism was considered by some to be due at first to the slight fever, and later to the sore throat, tonsillectomy, or to nervousness. Others thought the whole picture was one of mitral stenosis with transient auricular fibrillation. After a month's delay, with the condition remaining unchanged despite digitalization, he was started on Lugol's solution and the metabolism fell to plus 26. A hemithyroidectomy was then performed January 22, 1929 by the surgeon who previously refused to operate because of the uncertainty of the diagnosis. The pathological report of this tissue showed parenchymatous hyperplasia of the thyroid gland.

The day following the operation, as frequently happens, another attack of transient auricular fibrillation occurred. He was discharged shortly after this and was told to return in about six weeks for a second operation, which was performed on March 26, 1929. He again had an attack of transient fibrillation, and then had an uneventful convalescence. The patient improved a great deal subsequently. He gained seventeen pounds, but continued to have occasional attacks of palpitation. The metabolism reading remained constantly elevated at about plus 20, although the pulse rate ranged between 64 and 80. Several months later he

cause of a maintained elevation in the metabolism, a third operation was performed. After this the metabolism fell to plus 4 and stayed at a normal level. The patient has since returned to work and feels well.

### SUMMARY

This is an instance in which the differential diagnosis lay between mitral stenosis and hyperthyroidism. The obscurity of the diagnosis was well indicated by the difficulty in convincing both internists and surgeons that the thyroid was toxic. One unusual feature was the slow heart rate which often ranged between 67 and 70, even when the metabolism was markedly elevated. The appearance of the face, the transient auricular fibrillation, the hyperdynamic character of the heart sounds and the slight glycosuria, all pointed, however, to a latent hyperthyroidism. Three operations were necessary because the surgeon did not remove enough thyroid tissue the first two times.

*Case 6* P. C., a 48 year old longshoreman, entered the hospital January 29, 1929, complaining of cough, pains in the chest, weakness and dyspnea. He previously was well and strong, doing hard work until two years ago, when he had a vomiting spell which lasted two weeks. At this time he was studied very carefully at a large general hospital. On discharge the vomiting had ceased, but he was not able to work since then because of weakness. About a month ago he grew worse, began to vomit again, complained of pains in the chest and was very short of breath. There was no previous history of rheumatic fever or chorea.

Examination at this time showed a markedly emaciated man with a rather sickly appearance. The heart was considerably enlarged, the rhythm grossly irregular and the sounds were hyperactive in quality. There was a loud somewhat musical systolic

murmur at the apex. No diastolic murmur could be heard. The blood pressure was 140 mm systolic and 78 mm diastolic. Numerous moist râles were heard at both bases. The liver was slightly enlarged. There was no exophthalmos, or tremor of the fingers, and the thyroid gland was not palpable. The urine was negative. The blood showed a slight leucocytosis, but otherwise was normal. The Wassermann was negative. The most striking feature was the appearance of the skin, which was quite typical of this entire group of patients. It was warm, moist, hyperemic and somewhat pigmented. The hair was prematurely gray.

During the first week in the hospital the temperature ranged from 99 to 101, and then the fever gradually disappeared. The heart rate ranged from 100 to 120. Many basal metabolism tests were made during the subsequent weeks. At first the readings were between plus 40 and plus 50, later they ranged from plus 25 to plus 35. For three weeks, no specific therapy was administered except digitalis. Although generally he improved, in that the fever, cough and pain disappeared, the heart rate remained rapid, and he lost a few pounds. The day Lugol's solution was started (February 22, 1929) his weight was 87 pounds. During the following three weeks, the heart rate slowed slightly, and the lowest metabolic reading was plus 19.

This case attracted considerable attention and was seen by a great many physicians. For over two months none of the observers would believe that this patient was suffering from thyrotoxicosis. He had been previously studied with extreme care at another hospital and the report from there illustrates the difficulty in diagnosis. This read, "Diagnosis: Fever of unknown origin, ? spinal cord lesion, rheumatic heart disease with mitral stenosis, ? tuberculous peritonitis. This patient from the start has been a complete puzzle to us. He was seen in consultation by the Senior of the following services: Throat, Surgical, Neurological, Psychiatric, Cardiac, Neurosurgical, Orthopedic and Medical, and in no instance was their finding such as to account for the patient's symptoms."

It was not until after clinical improvement followed the administration of Lugol's solution and the subsequent development of a definitely palpable goiter, that the original diagnosis of thyroid heart disease was accepted. He then was given two X-ray treatments over the thyroid gland during March, but the basal metabolism remained moderately elevated (about plus 30). On April 18 a hemi-thyroidectomy was done. Pathological examination of this showed parenchymatous hyperplasia of the thyroid gland. His condition was quite critical a few days after this, but then he gradually improved. After the operation the metabolism tests were normal (minus 6 to plus 8). The patient felt a great deal better and became ambulatory. His weight increased from 87 to 110 pounds. Auricular fibrillation continued, but as weeks went on it was found that the metabolism tended to rise and then remained fixed at plus 25%. A second operation was therefore performed which cured the hyperthyroidism. After this the metabolism remained normal and the auricular fibrillation was made to disappear by the use of quinidine.

### SUMMARY

This patient had an active thyrotoxicosis for several years. Although a great many tests and observations were carried out, a basal metabolism determination was not previously done. Prominent heart consultants considered the condition as mitral stenosis. The removal of the cause of the intoxication of the heart was delayed because of failure in diagnosis, although eventually marked improvement resulted from the thyroidectomy.

*Case 7.* H. S., a man 44 years old, was seen on June 20, 1927, complaining of shortness of breath. For eighteen months previously he had increasing dyspnea on exertion and palpitation. There was no loss of weight. During this illness, he had to gradually restrict his activities. During the last months he was more or less confined to his home and at various times he was in bed. During the last month he found it diffi-

cult to stay in bed and had to sleep sitting up in a chair. Latterly, he noticed a troublesome cough and edema of the feet. On direct questioning, he admitted that for two years he had been nervous. In the past history it was learned that he never had rheumatic fever or chorea, but at the age of twenty a doctor told him he had heart disease. During this eighteen month's illness he was treated by a heart specialist, but steadily grew worse. Although at times he would improve slightly with rest in bed, he never properly responded to digitalis therapy, for the heart rate continued to be rapid. On several occasions he discussed the advisability of consultation, but the cardiologist repeatedly told him that nothing more could be done for him by anyone, and that he would merely waste his money, most of which he gradually spent on medical care.

He entered the hospital June 23, 1927. On examination he showed typical evidence of mitral stenosis, auricular fibrillation and congestive heart failure. The heart was moderately enlarged and was grossly irregular in action, with a rate of 180, and the first sound markedly accentuated. There was a systolic murmur all over the precordium and a definite diastolic rumble at the apex. A short thrill could be felt at the apex which was difficult to time. The bases of the lungs showed evidence of free fluid, more so on the left. The liver was moderately enlarged and slightly tender. There was considerable pitting edema of the lower back and the legs. The thyroid gland could not be felt, and there was a questionable tremor of the fingers. The sclerae showed a definite icteric tint. At first the diagnosis of hyperthyroidism was overlooked, but it was soon noticed that the skin was warm and moist, and there was a slight increased pigmentation of the upper chest, neck and face. A metabolism test was therefore done and found to be plus 61%. The blood Wassermann was negative, the urine was essentially negative, and there was a slight leucocytosis.

Having decided that he had latent hyperthyroidism, he was given Lugol's solution drops 10, three times a day. He was also given digitalis. During the following two weeks a most dramatic improvement took place. The apex rate gradually fell from 180 to 70. The temperature of 100 per-

sisted for one week, and then became normal. A striking diuresis occurred, with a gradual disappearance of all signs of congestion. The consecutive metabolism readings were plus 21, plus 12 and plus 7, during this period. The patient felt much better than he had for two years. A subtotal thyroidectomy was performed on July 9, 1927. The gland was found to be only slightly larger than normal, but the pathological report showed marked hyperplasia, and in one area a small adenoma. Inasmuch as he felt so well before the operation, it is hard to say that he was any better after it. Auricular fibrillation continued, and so he was given quinidine sulphate for a few days, and on July 22, while taking 6 grams, three times a day, the heart became regular. Inasmuch as the fibrillation recurred, quinidine was omitted, and he was kept on constant digitalis. The patient was discharged in excellent condition, and he returned to work, which he has been carrying on ever since.

#### SUMMARY

This case illustrated very well the difficulties that arise when a patient has both mitral stenosis and hyperthyroidism. The features of one are so much like those of the other that confusion easily results. A cure of the hyperthyroidism merely relieved the heart, already burdened with mitral stenosis, of an added load. The improvement thereby obtained was most extraordinary. Here again a latent hyperthyroidism was detected because of the general appearance of the patient, and the failure to obtain the customary slowing of a fibrillating heart with digitalis.

*Case 8* C. K. H., aged 57, entered the hospital May 23, 1929. He considered himself in good health until the middle of April, since when he noticed increasing weakness. A little later he became somewhat short of breath and hoarse. On May 14, he saw his physician with regard to having a tonsillectomy performed. At this time, the doc-

tor found his heart rapid and irregular. He gave him one and one-half grains of digitalis three times a day, and the patient was put to bed. A week before this he developed attacks of fainting. He would almost lose consciousness, would feel a "wave" running over his body, at the same time becoming dizzy. These became more numerous under digitalis. There never was any pain. He lost about five pounds in weight. His appetite had been fair, and he never noticed palpitation. The patient and the family never thought that he was nervous.

When he was seen in consultation on May 21, 1929, it was found that his heart rate was 39 at one moment, and a few minutes later it was 60, at both times quite regular. There was a slight apical and basal systolic murmur. The first heart sound was accentuated. The blood pressure was 112 mm systolic and 75 mm diastolic, and the rest of the examination was essentially negative except for the appearance of the patient's face. The skin was warm, moist, hyperemic and distinctly salmon-colored. The thyroid gland could not be felt at all. There was no exophthalmos but there was a distinct tremor of the fingers. The diagnosis at this time was heart block, Adams-Stokes syncope, and probably latent hyperthyroidism. He was sent to the hospital for further study.

In the hospital he was found to have a metabolism of plus 51 on May 24, 1929. The blood pressure was 126 mm systolic and 64 mm diastolic. The urine was negative except for a slightest possible trace of sugar on one occasion. The Wassermann was negative. The blood was normal except for a distinct lymphocytosis. The X-ray of the hands showed moderate, diffuse decalcification of the bones. He was put on 10 drops of Lugol's solution, three times a day. Subsequent metabolism readings showed a marked fall on May 25, 1929, plus 27 on May 28, 1929, plus 10 on May 31, 1929 and plus 16 on June 3, 1929. During the iodine medication the patient generally felt much better. He gained about 13 pounds of weight, which was suspected to be partly due to retention of water, although no evidence of edema could be made out. However, he developed frequent syncopal at-

tacks. Before these occurred, a transient attack of auricular fibrillation, with a heart rate of about 100 took place. When the metabolism was at its lowest, the mild spells of syncope were frequent. The heart rate then ranged between 40 and 50, and there were frequent pauses of the heart of three to eight seconds. Electrocardiograms showed this to be due to sinus pauses, and not to any blocking of the beats. In other words, the impulses were actually not formed during these pauses. He was given one milligram of atropine sulphate subcutaneously, but the bradycardia and the pauses continued. On June 1, barium chlorid 30 milligrams, four times a day was started. The heart rate remained slow after this, but the attacks of syncope were distinctly less frequent. On June 3 one cc. of adrenalin was given subcutaneously after which he had a transient spell of auricular fibrillation.

On June 5, a subtotal thyroidectomy was performed, and the gland was found to be a great deal larger than was anticipated. The lateral lobes were found along the posterolateral surfaces of the trachea. Following the operation he had a well marked diuresis, which indicated that previously he had retained fluid. During the first twenty-four hours he had a few minor syncopal attacks, but after this they never recurred. The metabolism on June 15, 1929 was minus 2. His clinical improvement was most striking. The heart remained slow and regular, he began to gain weight, and voluntarily remarked that he felt much better than he had for some months. He shortly returned to work and has been well in every way since.

#### SUMMARY

This was a most unique experience, as I am unfamiliar with any instance in the medical literature in which Adams-Stokes attacks were associated with hyperthyroidism. The diagnosis was first suspected and later confirmed, at a time when the patient had a heart rate of 39, because of the features repeatedly emphasized in this paper, despite the absence of exophthalmos or any palpable thyroid whatever. The therapeutic result was most gratifying.

#### SUMMARY AND CONCLUSIONS

1 Attention is drawn to a group of patients usually treated for heart disease, in whom the underlying cause is a latent and unrecognized hyperthyroidism. These cases are generally overlooked, even by most competent internists, for the common signs and symptoms usually found in typical exophthalmic goiter and toxic adenoma are not evident in these patients.

2 The diagnosis is even more difficult in patients, who have co-existing organic heart disease, such as angina pectoris, hypertensive heart disease or mitral stenosis. Of special interest are those with typical anginal attacks, in whom proper treatment of the latent hyperthyroidism results in a great reduction in the number of attacks, if not complete relief from symptoms.

3. The diagnostic criteria are discussed and attention is especially directed to certain points in the general appearance of the patient and in the physical findings that lead one to suspect the presence of a latent hyperthyroidism.

4 Circulatory insufficiency is not a contraindication for surgery in the treatment of these patients, many of whom are relieved completely, and others much improved by subtotal thyroidectomy.

5 A series of cases is reported, all of which had been treated for a considerable period of time for heart disease, but in each of which there was an unrecognized hyperthyroidism either as the sole cause of the trouble, or as an additional burden on a heart already affected with some other organic lesion. In every case either complete cure or marked improvement was obtained, when treatment was directed at the previously unsuspected thyroid gland.

# Lead Poisoning in the English Books of Trades\*†

CARL VERNON WELLER, M S , M D , *Ann Arbor, Michigan*

THE Books of Trades attempt to give "Parents, Guardians and Trustees, as well as the Youths themselves, intended for Trades and Business, not only a general Description of almost all Handicrafts, Trades and Employments in Vogue, but also such Particulars of them, as will enable both the one and the other to form a tolerable Judgment which of them all may be most agreeable, and best answer their purpose" (Preface to 'A General Description of All Trades', 1747) If these prefatory promises were completely fulfilled the Books of Trades ought to reflect the state of knowledge of occupational disease at the times at which they were written, for one phase of the guidance promised the parents and trustees was to warn them of the hazards to be met in the various callings

A group of these popular guides to the choice of a trade or business has been examined for evidences of knowledge that employment in those trades in which lead and lead compounds were used entailed a special possibility or probability of physical ills. Four Books of Trades ranging in date of printing from 1747 to 1837 have been used for this purpose. In order of publication these are

1 A General Description of all Trades, Digested in Alphabetical Order, etc , Printed for T Waller, 1747

2 The Book of English Trades and Library of the Useful Arts Printed for G and W B Whittaker, 1824

3 The Book of English Trades and Library of the Useful Arts Printed for J G and F Rivington, 1835 (Much of the text of this book is identical with that of the preceding )

4 The Complete Book of Trades, or the Parents' Guide and Youths' Instructor, Forming a Popular Encyclopaedia of Trades, Manufactures, and Commerce, as at Present Pursued in England, etc , By Several hands, viz Mr N Whittock, Mr J Bennett, Mr J Badcock, Mr C Newton, and others 1837

References which may be fairly interpreted as referring, perhaps unconsciously, to the hazards of lead poisoning will be quoted in full under each trade where such occur, except that verbatim duplications will not be repeated. The books will be referred to by using their respective dates of publication.

## *Color Men*

The business of the color men, the risk to health involved in this trade and the means to be made use of to avoid ill effects are all sufficiently set forth in the 1747 book, as follows

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\*From the Department of Pathology, University of Michigan, Ann Arbor, Michigan

†Read before the American Association of the History of Medicine, May 7, 1930



A  
**GENERAL DESCRIPTION**  
 OF ALL  
**TRADES,**  
 DIGESTED IN  
**ALPHABETICAL ORDER:**

BY WHICH

**PARENTS, GUARDIANS, and TRUSTEES,**  
 may, with greater Ease and Certainty, make choice  
 of **TRADES** agreeable to the Capacity, Education,  
 Inclination, Strength, and Fortune of the **YOUTH**  
 under their Care.

CONTAINING,

- |  |   |
|--|---|
| <p>I. How many Branches each is divided into.</p> <p>II. How far populous, or necessary.</p> <p>III. Which they require most, Learning, Art, or Labour.</p> <p>IV. What is commonly given with an Apprentice to each.</p> <p>V. Hours of Working, and other Customs usual among them.</p> <p>VI. Their Wages, and how much</p> | <p>may be earned by, or is commonly given to, Journey-men.</p> <p>VII. What Money is necessary to set up a Person in each.</p> <p>VIII. Which are incorporated Companies, with the Time of their Incorporation, Li-verry-fine, Situation of their Hall, Court-day, Description of their Arms, Mottos, &amp;c.</p> |
|--|---|

To which is Prefixed,

An **ESSAY** on **DIVINITY, LAW, and PHYSIC.**

---

**L O N D O N:**

Printed for **T. WALLER**, at the *Crown and Mitre*,  
 opposite *Fetter-lane, Fleet-street.* M DCC XLVII.

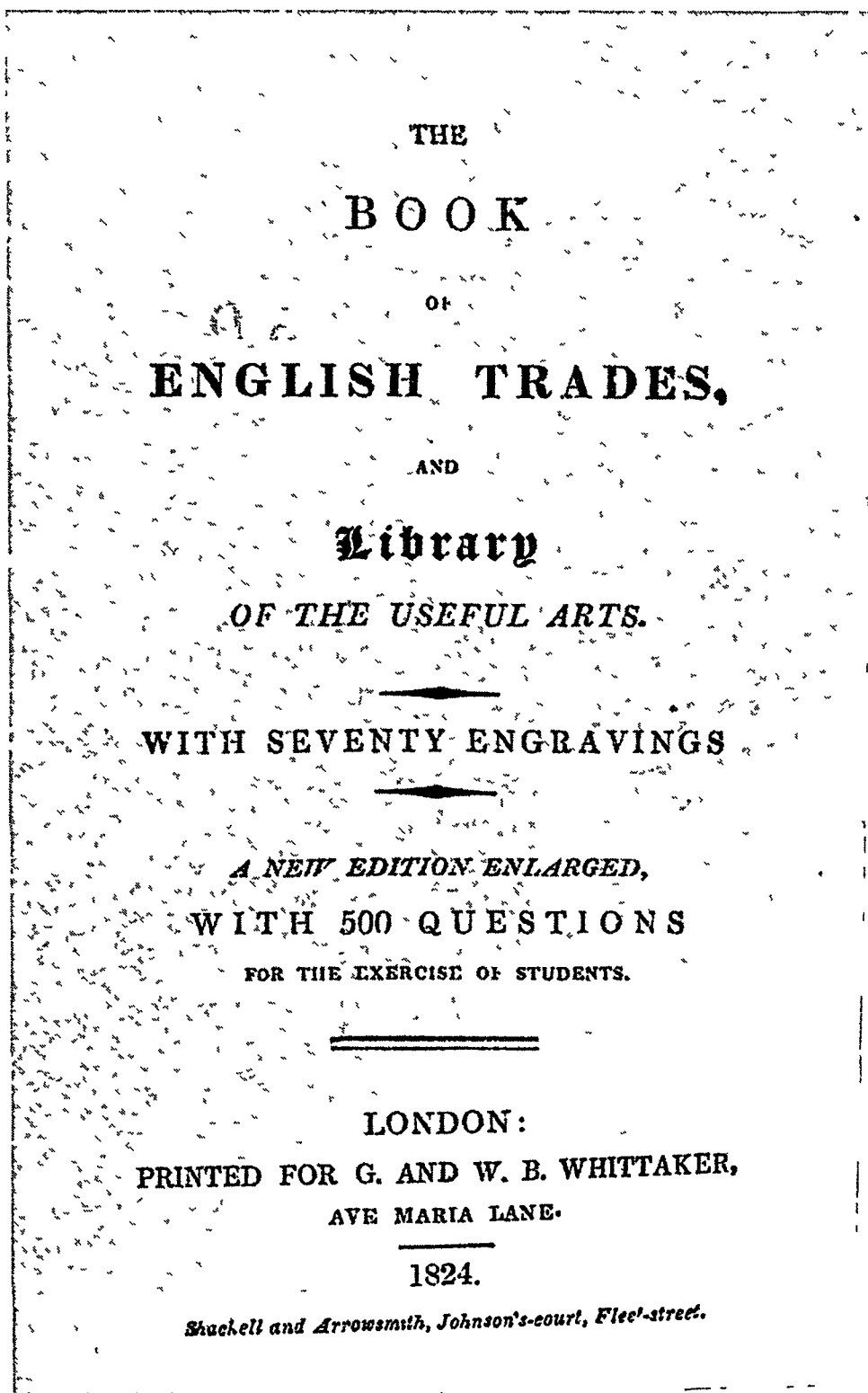


FIG 2 Title page of the Whittaker book of trades, 1824

THE BOOK  
OF  
ENGLISH TRADES,  
AND  
LIBRARY OF THE USEFUL ARTS.  
  
WITH EIGHTY-SIX WOOD-CUTS  
  
NEW EDITION  
  
LONDON  
PRINTED FOR J. G. & F. RIVINGTON,  
*Booksellers to the Society for Promoting Christian Knowledge,*  
ST PAUL'S CHURCH YARD, AND WATERLOO PLACE, LALL HALL  
1835

FIG 3 Title page of the Rivington book of trades, 1835

THE COMPLETE  
**BOOK OF TRADES,**  
 OR THE  
 PARENTS' GUIDE AND YOUTHS' INSTRUCTOR,  
 FORMING A POPULAR  
 ENCYCLOPÆDIA OF TRADES, MANUFACTURES,  
 AND COMMERCE,  
 AS AT PRESENT PURSUED IN ENGLAND,  
 WITH A  
 MORE PARTICULAR REGARD TO ITS STATE IN AND NEAR THE  
 METROPOLIS  
 INCLUDING  
 A COPIOUS TABLE OF EVERY TRADE, PROFESSION,  
 OCCUPATION, AND CALLING,  
 HOWEVER DIVIDED AND SUBDIVIDED  
 TOGETHER WITH  
 THE APPRENTICE FEE USUALLY GIVEN WITH EACH,  
 AND  
 AN ESTIMATE OF THE SUMS REQUIRED FOR COMMENCING  
 BUSINESS  
 BY SEVERAL HANDS  
 MR N WHITTOCK, MR J BENNETT, MR J BADCOCK,  
 MR C NEWTON, AND OTHERS,  
 AS MORE PARTICULARLY SET FORTH IN THE PREFACE

LONDON

PUBLISHED FOR THE PROPRIETOR BY  
 JOHN BENNETT, 4, THREE TUN PASSAGE IVY LANE,  
 PATERNOSTER ROW,  
 AND SOLD BY  
 SIMPKIN, MARSHALL, & CO, STATIONERS' HALL COURT

1837.

FIG 4 Title page of the Whittock book of trades, 1837

"The preparing and selling of all Sorts of Colours, Paints, Oils, and Varnishes, for the Use of Painters, Japanners, etc., is their Business, for which Purpose some keep large Shops and Warehouses, though they are not numerous, and it is a Branch of Trade in which there is much Profit, though somewhat hazardous to Health, especially if a Lad is not particularly careful to keep himself as clean as possible, nay, indeed, every one concerned in any Part of it ought to be so, which would prevent a great many Inconveniences. However, it is by no means fit for weakly Constitutions."

The nature of the affections common to this trade is not revealed. One might

believe that the volatile solvents were concerned were it not for the fact that personal cleanliness is so strongly recommended as a preventive measure. This trade is not listed in the later books examined.

### *Painters*

The book of 1747 has but one short paragraph dealing with the diseases peculiar to painters. "House and Ship-painters' Work is by far the more populous, but the heaviest, and requires the most Care with respect to Cleanliness, they being often liable to nervous Disorders, occasioned by the Colours they use so much more of than the others." This is an undoubted reference to lead poisoning.



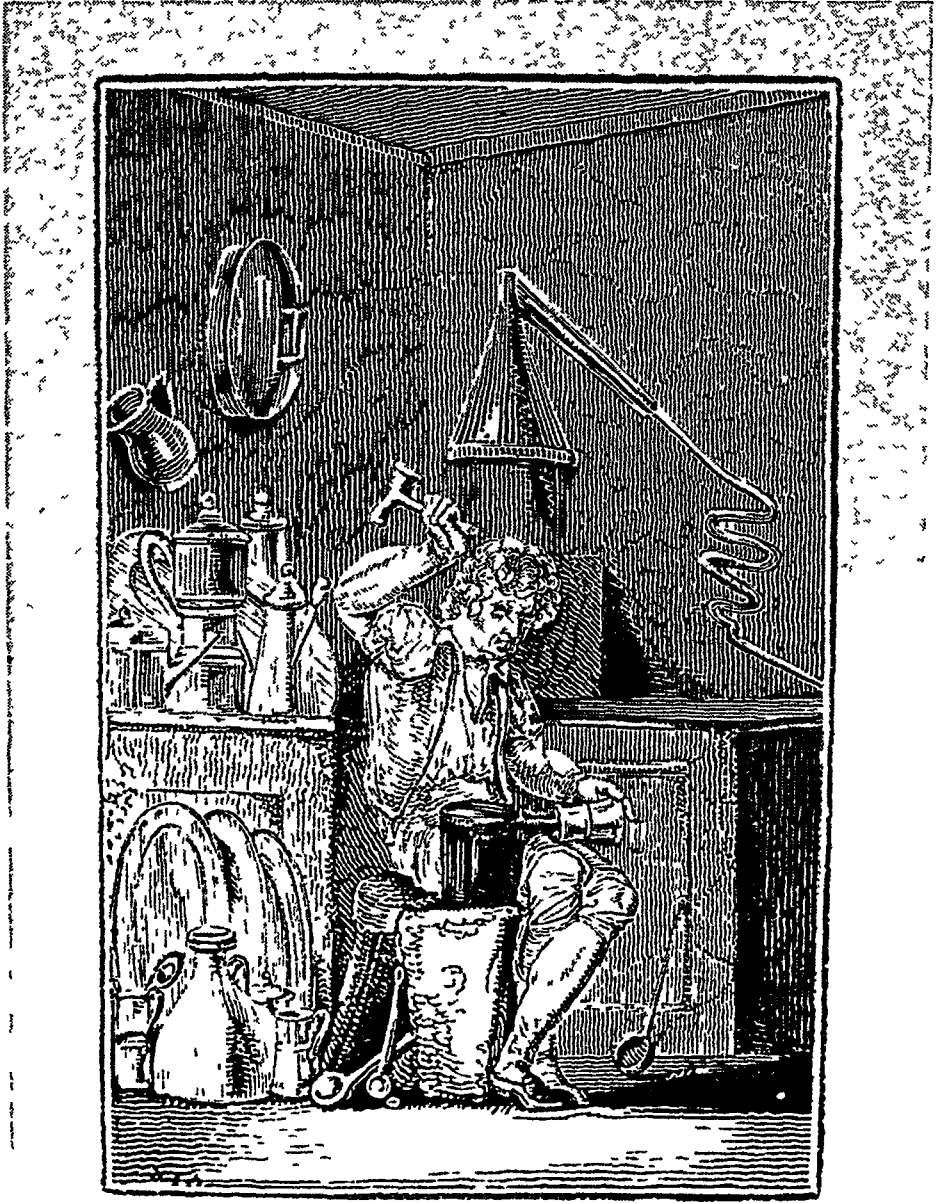
FIG 5 The House Painter, from the Whittock, 1837, book of trades

In 1837 the warning is much more forcibly given. After emphasizing the importance of a clear head while working at an elevation on scaffolding or ladders, and warning against the excessive use of the "oft replenished porter-pot" lest the painter fall to use no more, the writer continues "To this catastrophe he would the more assuredly tend, if, in the course of mixing and handling his colours, he do not carefully abstain from too close contact with the very deleterious compound of turps (turpentine) with the white lead, whence a noxious effluvia arises, but, whether by one means or the other, or with the addition of oil, or verdigris, he imbibes, takes up, or absorbs, into his bodily system, any of these, his limbs become paralyzed, he loses strength, and becomes a walking mummy, unless he previously loses firm hold on the frail supports of his person while at work, and he finish his career in the twinkling of an eye. Our duty towards the reader would have been performed imperfectly, but for this friendly premonition. The Painters of the present day, however, perform the principal part of the operation of grinding by means of mills, carried by *horse power*, which lessens the labour, truly, but still much remains of danger from the tipping carelessness of most of the men, though every one of them says he is perfectly aware of his danger, and well apprized of the means of prevention. These are, cleanliness of the person, particularly of the hands, and averting the head—the olfactory, upon pouring on the turps upon the white lead, changing clothes, linen and locality, after the

work is over, etc., adds to the security from the paralytic attack, from which even a visit to the Bath waters cannot always relieve him, let Dr Davis say what he may think proper on the occasion. We should hear with perfect indifference, the usual parting remark to one of those afflicted poor painters 'You have had the benefit of the Bath waters, my man, and nothing more can be done for you,' for, we have inquired in vain for one successful case of such paralysis from the use of those celebrated waters. There, we have often seen long strings of such poor creatures, crawling to the bath, and have found numerous other painters in London who have tried them, without the desired effect." From all of this it will be seen that the writer had some notion of lead palsy and lead cachexia and no good opinion at all of the efforts of contemporary Medicine to cure or even relieve these afflictions. He was aware, also, of the great importance of personal cleanliness in preventing the development of lead poisoning.

#### *Pewterers*

The danger involved in the use of pewter containing too high a proportion of lead was early recognized. At Nuremberg in 1576 it was ordained that not more than one pound of lead should be mixed with every ten pounds of tin. In England regulatory provisions governing this matter were drawn up as early as 1348. At first as much as 26 pounds of lead could be used with each hundred weight of tin but the amount was soon greatly reduced. The 1747 Book of Trades is silent upon this question, calling at-



*Pewterer.*

FIG 6 The Pewterer, from the Rivington, 1835, book of trades

tention only to the fact that the business of melting, casting and turning pewter is "not so healthy" But in 1824 it is more fully set forth "Lead being the cheapest (sic!) of the two metals, the manufacturer finds it his interest to employ it in as large a proportion as possible But as lead is well known to be a very noxious metal, experiments have been made to ascertain in what proportion it may be mixed with tin, without injury to

the liquors for which pewter is commonly used It has been found, when wine or vinegar was allowed to stand in vessels composed of an alloy of tin and lead, that the tin is first dissolved, whilst the lead is not acted upon by the liquors, except at the line of contact of the air and liquor, and that no sensible quantity of lead is dissolved, even by vinegar, after standing for some days in vessels that contained no more than eighteen pounds in the

hundred of lead. Hence it was concluded, that as no noxious effect is produced by the very minute quantity of tin which is dissolved, pewter may be considered as perfectly safe, which contains about 80 or 82 per cent of tin. And when vessels are employed for measures, a much less proportion of tin may be used. But it has been found that the common pewter at Paris, contains no more than about 25, or 30 per cent of tin, the remainder is lead, and there is great reason for believing that the pewter commonly used in England is of no better quality. It is evident, therefore, that the use of pewter vessels, unless the proportion of the alloy could be ascertained, is by no means desirable."

In the article dealing with the pewter in the fourth book of the series under examination, that of 1837, even the comparative safety of those alloys containing a low percentage of lead is questioned, and the danger to both the artificer and to the user is set forth.

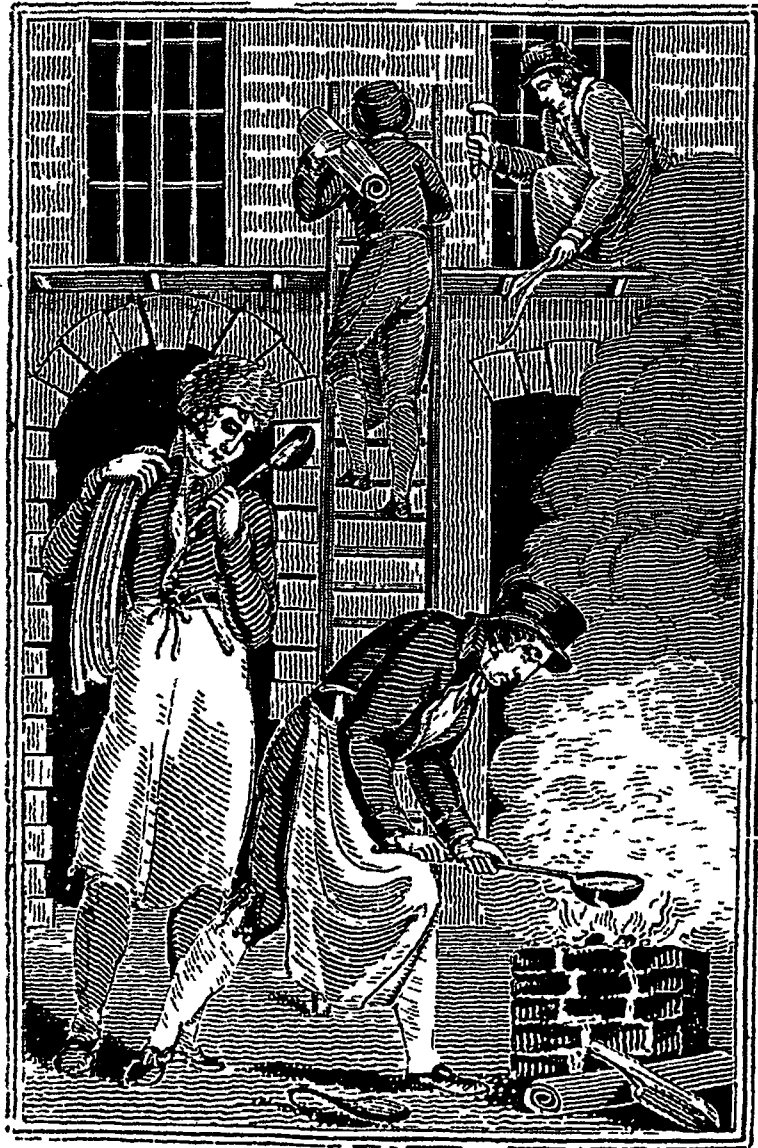
"Pewter is composed of tin and lead, or lead and the regulus of antimony, in proportions of ten, twelve, or fourteen of the softer to one of the harder metals. We also hear of pewter being compounded of all three of these simple metals, but mix them how you may, and though zinc be added, the poisonous nature of all, whether separate or combined, cannot be denied." After commenting on the constant occurrence of arsenic in the tin, "the least objectionable of all", the writer continues - "Let these poisons repose how they may in your utensils, when the contained liquids are employed *cold*, the proportion of

20 or 25 per cent of tin (if the proportions ever reach so high), cannot divest the lead of its deleterious nature, especially when used with acetic acid. Spoons, plates, etc., give out the sugar of lead (*sacch. plumbi*) whenever vinegar is applied to the salad, to cucumber, to oyster, or to meats, —with fatal consequences. In whatever manner the workmen are engaged in melting, forming, or handling any of these metals, together or separately, they lose health, become pale, experience visceral derangement and intumescence, or fall into paralysis—in the degree that their contact, or exposure to the melting fumes, may be more or less."

#### Plumbers

In 1747 the work of plumbers is described as having to do with keeping out the rain and with conveying and storing liquids. "It cannot be called very hard Work, the casting Part whereof is the heavier, apt to render the Labourers in it unhealthy (without Care is taken to be cleanly) and sometimes hazardous." In 1824 the warning is more strongly put - "The health of the men is often injured by the fumes of the lead. Journeymen earn about thirty shillings a week, and we recommend earnestly to lads brought up to either of the before-mentioned trades [painter, plumber], that they cultivate cleanliness and strict sobriety, and that they never, on any account, eat their meals or retire to rest at night, before they have well washed their hands and face." Under this heading the Whittock Book of Trades of 1837 has but one sentence dealing with this disease





*Plumber.*

FIG 7 The Plumber, from the Rivington, 1835, book of trades

hazard "Under the article Painter, we have noticed the danger to health which is to be apprehended from the volatilized fumes from lead, and the same remarks apply to the casting of sheet-lead, pipes and melting of solder which constitute the trade of a Plumber."

#### *Potters*

It is remarkable that the only reference to the health hazard for pottery workers in these four Books of

Trades is to be found in the earliest, that of 1747, and this is but a feeble warning in one parenthetical explanation - "The Masters in all the Branches (none of which can be called very hard Work, though not the most cleanly Employ, and apt to render the Workmen unhealthy if not careful) take apprentices" Can it be that the complete lack of discussion of the question in the later books of much larger size means that the physical ill-

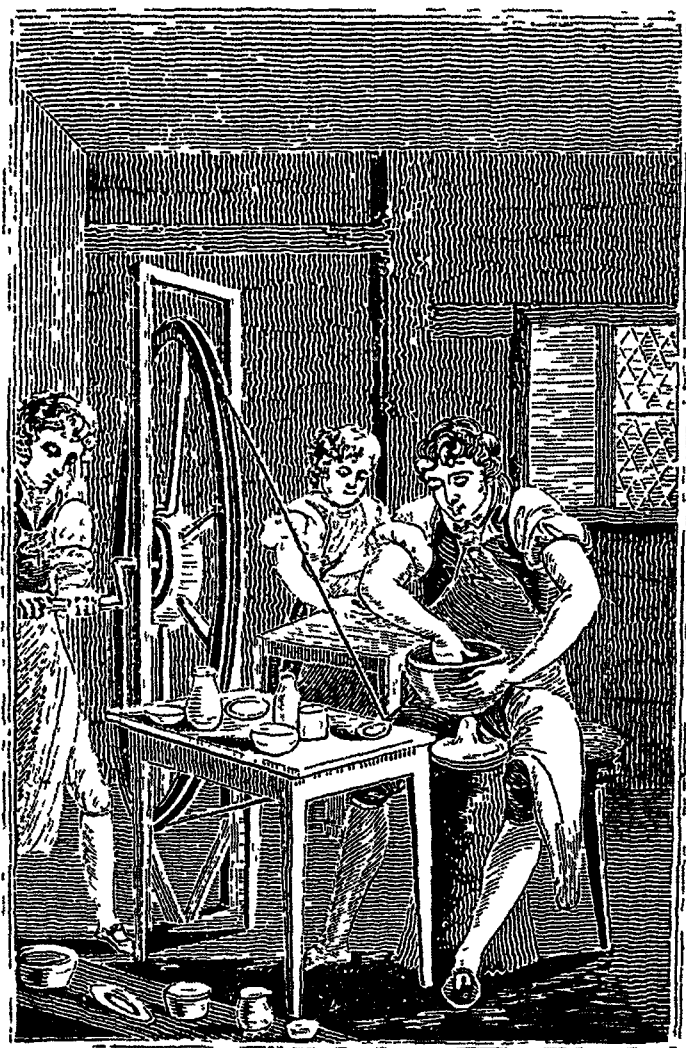
*Potter*

FIG 8 The Potter, from the Rivington, 1835, book of trades

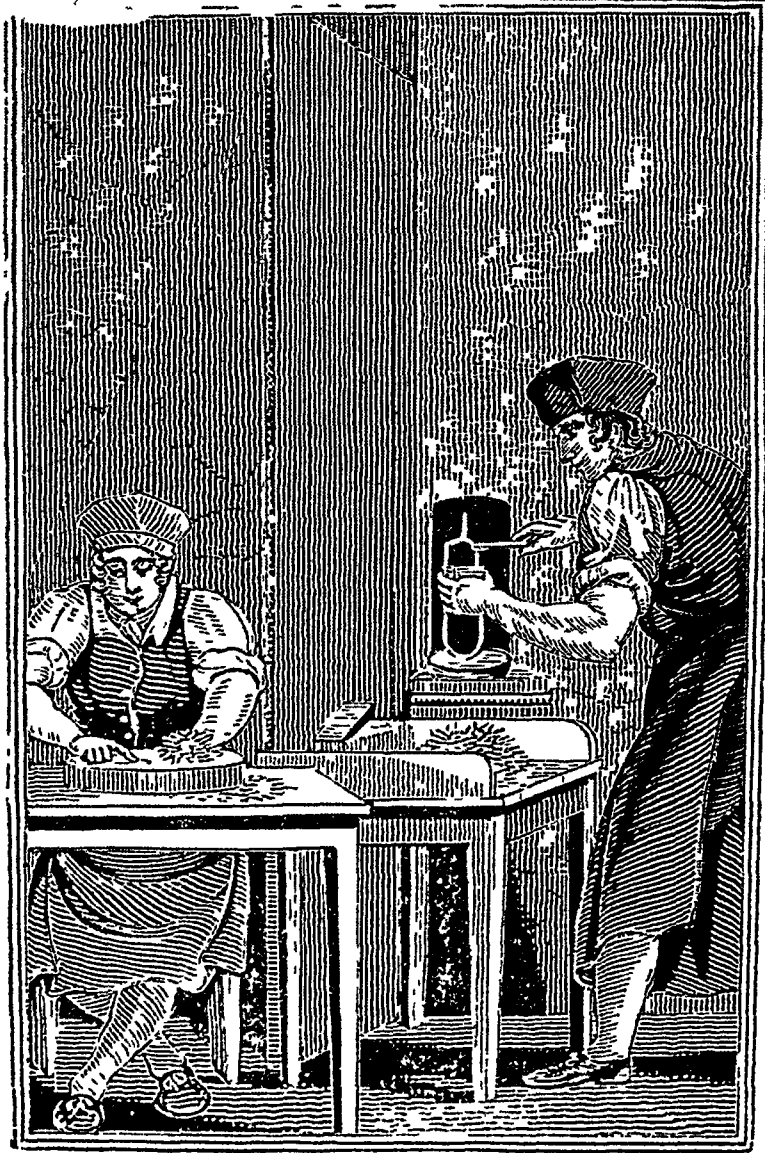
common to potters were so well known that they were taken quite for granted?

#### *Printers and Typefounders*

In the discussion of the Printer's activities there are no references which can be interpreted as having to do with lead poisoning. In the book of 1824, however, there is a brief reference to the hazard of fumes from the molten type metal "In

large foundries this metal is cast into bars of about twenty pounds each, which are delivered to the workmen as conditions may require, this is a laborious and unwholesome part of the business owing to the fumes which are thrown off."

When contemporary knowledge of occupational diseases and of lead poisoning especially is considered, it is surprising that these Books of Trades have such a relatively small



*Type Founder*

FIG. 9 The Type Founder, from the Rivington, 1835, book of trades

amount of material upon the subject. In 1700, forty-seven years before the first of these books, Ramazzini's *De Morbis Artificum Diatriba* had appeared. This had been put into English by 1705 and had passed through various editions in that language, as well as sundry Latin editions printed in England. In this work the diseases of Potters and of Painters are described in great detail and certain signs and symptoms correctly ascribed

to lead poisoning. Ramazzini's book was the standard text upon occupational diseases during the period covered by these Books of Trades. Long before this time Citois had described Pontou colic and Stockhausen had shown that this condition was produced by lead in various forms.

Why did not the writers of the English Books of Trades take advantage of this knowledge of trade diseases? Several answers to this question

tion present themselves. In the first place these books are the most obvious hack writing, copied to a greater or less extent one from another and running through many editions with but slight addition of new material. They were intended for popular sale and so were kept small and inexpensive. In the second place there is no evidence that any of the various authors had had medical training or had sought medical collaboration. On the contrary, it is made clear in the extensive quotation from the article on Painters in the book of 1837 that the particular author responsible for that section was far from being sympathetically inclined toward the medical activities of his own period. Then, too, there is an evident desire not to

describe any one trade in such a condemnatory manner as to discourage entirely the young man from entering upon it. If unfavorable conditions are referred to, something on the opposite side is introduced to balance the scale. The authors had no desire to arouse the antagonism of any group of tradesmen. Finally, we must believe that certain hazards were so obvious, so much a matter of daily experience, that they were taken for granted then as others are now and were therefore not described. Such must have been the reason why the English Books of Trades failed in such a large measure to equal the medical works of their period in regard to descriptions of industrial lead poisoning.

## Editorials

### *THE TREATMENT OF PER- NICIOUS ANEMIA WITH STOMACH AND STOM- ACH EXTRACT*

Some time ago in these columns we referred to a preliminary report of Sturgis and Isaacs on the treatment of pernicious anemia with desiccated hog's stomach. Although in the three patients to whom this treatment had been given there was observed a typical marked reticulocyte reaction, with a typical increase of the hemoglobin and red blood cells, it was felt that the number of cases reported did not form a sufficient foundation on which to base definite judgment as to the value of the new treatment, especially since on the basis of their meagre observations Sturgis and Isaacs were inclined to the opinion that the stomach treatment was more active than that of the liver. Confirmation of their results appeared in a communication by Conner, who treated six cases of pernicious anemia with swine stomach, and also by Wilkinson, who found both the mucosa and muscularis to be potent. Further confirmation of the results obtained by Sturgis and Isaacs has been recorded in short reports by Hitzemberger, Snapper and Dupreez, and Rosenow. Recently E. Meulengracht and A. Hecht-Johansen, of Copenhagen\* have reported four cases of pernicious anemia treated

with dried, pulverized swine stomach. Their preparation was made according to the method of Sturgis and Isaacs: whole, fresh swine stomachs, both mucosa and muscle coats, were quickly dried at low temperature, the fats removed by benzine, and the residue pulverized and passed through a sieve. There remains a whitish-gray powder, 30 gm of which corresponds roughly to about 200 gm of the fresh tissue. The powder has a slight odor, but is practically tasteless. The powder was administered by mixing 10 gm with raspberry juice to a thin mixture in the bottom of an ordinary water glass, which was then filled up to one-third of its content with cold water. In this form it was taken with relish by the patients. In daily doses of 20-30 gm, corresponding to 130-200 gm of whole swine stomach, this dried stomach substance has a powerful therapeutic action on pernicious anemia. Whether more potent than liver could not be determined at this time, but these workers regard this as not improbable. On the other hand, an extract of swine stomach, even in doses corresponding to 400 gm of whole swine liver, given daily was found to be negative. This observation has great theoretic interest, in that it would appear that the active principle is not preformed ("aufimagerisiert") in the stomach, but is found, or set free, only after the powdered

\**Die Wochenschr.* Jan. 24, 1930

stomach, which contains both the mucosa elements and the muscle-protein from the muscularis, is introduced into the intestinal canal. This confirms Castle's original experiments, upon which all the stomach work has been based, that the natural stomach-juice does not contain the active principle, but that this is first produced, only when the gastric juice acts upon muscle. To go back to Castle's experiments, he found that muscle (meat) digested in the human stomach, or in vitro with normal gastric juice obtained from the normal stomach after injection of histamin, contained the same active therapeutic principle for pernicious anemia as that found in liver, as shown by its administration to pernicious anemia patients. The active principle, however, could not be produced in vitro with pepsin + hydrochloric acid + meat, which led to the conclusion that the natural gastric juice contained something more than the pepsin, which is necessary for the formation of the active therapeutic substance during the digestion-process of the meat. From this, it was but logical to conclude that this necessary substance is lacking in the stomachs of patients with pernicious anemia. The lowered gastric function has long been recognized as one of the most fundamental phenomena of pernicious anemia, and the observations of Castle are to be counted as representing the most striking advance in our knowledge of the stomach condition in this disease. In spite of its brilliant results the liver treatment of pernicious anemia cannot be regarded as the final treatment of this disease. That this

is generally recognized is shown by the excessive zeal shown in the search for new methods of treatment. These attempts are motivated through the uncertainty as to the theoretic foundation of the liver cure, and its relation to the cord changes and other phenomena more or less constantly associated with pernicious anemia. For the present moment, it is, however, of great practical significance that dried, fat-free, pulverized swine stomach undoubtedly contains as active, or even a more active, therapeutic principle for pernicious anemia than does liver, since the cost of the stomach powder is far less than that of the liver extract. Castle's experimental work, and the clinical application by Sturgis and Isaacs, are of first importance in advancing our knowledge of the treatment of pernicious anemia beyond the stage of the Minot liver cure.

#### *THE SCOPE AND AIM OF THE COMMITTEE ON THE COST OF MEDICAL CARE*

At the spring meeting of the Committee on the Cost of Medical Care in Washington, May second and third, 1930, a special committee of private practitioners was appointed to consider the relation of the committee to the private practitioners of the country. This committee, composed of the undersigned members, now submits the following statement for the information of these practitioners on the scope and aim of the committee's work.

It was clearly recognized by all present at the spring meeting that the committee has undertaken a program of studies which in its scope goes far

beyond that part of the cost of medical care which physicians provide. The expense of several other kinds of service now looms large in the total cost of many illnesses. In addition, special emphasis was given at the meeting to the question of the adequacy of the various services available in a community. Finally, the committee adopted a statement of three fundamental principles proposed by the Chairman, which should go a long way toward reassuring those who have been apprehensive regarding the nature of the committee's ultimate recommendations.

### I

The committee is interested in far more than the physician's bill, which, in many instances, is considerably less than half the total cost of illness. Hospital care, nursing, dentistry, laboratory examinations, and medicines often involve considerable expense, as is clearly shown by several of the committee's studies which are now being completed or have already been reported upon. In one middlewestern county recently surveyed, the expenditures for various kinds of medicines constituted over one-third of the total expense for medical care, and were 20 per cent greater than the costs of physicians' services. It is also becoming apparent that a great deal of money is being spent for useless medicines and for various irregular forms of treatment which do the patient no good or which may result in positive harm.

In order to indicate clearly the broad scope of the committee's work, it was decided at the spring meeting

to make a slight change in its name. The word "cost" is to be changed to "costs." The complete name of the committee, with subtitle, will henceforth be "The Committee on the Costs of Medical Care—Organized to Study the Economic Aspects of the Prevention and the Care of Sickness, including the Adequacy, Availability and Compensation of the Persons and Agencies Concerned."

One vital problem before this committee, declared a prominent physician member, at the recent meeting, is the determination of what is reasonably adequate care. In many cases of obscure disorders and serious illness, expensive facilities are essential. Presumably, there must be available in the community well trained general practitioners, certain specialists, dentists, nurses, hospitals and health agencies,—trained and well equipped to do their part in providing all the care that the individual may need. A plan of the executive committee, to conduct a study to determine standards of adequate medical care, under the general direction of some well known competent physician and with the assistance of a committee of fifteen or twenty other physicians, was heartily endorsed at the meeting of the general committee.

The aim of the committee is to study the problem described by Dr. Olin West, the Secretary of the American Medical Association, as the one great outstanding problem before the medical profession today. This he says is that involved in "the delivery of adequate, scientific medical care to all the people, rich and poor, at a cost

which can be reasonably met by them in their respective stations in life" The committee is endeavoring to establish a foundation of facts which have an important bearing upon this problem. On the basis of these facts, it will propose recommendations for the provision of adequate and efficient therapeutic and preventive service for all the people at a reasonable cost to the individual, which, at the same time, will provide physicians, dentists, nurses, hospitals and other agents assurance of adequate return. This is not a new statement of aims. Recent discussion, however, has given new emphasis to certain aspects of it. There are important items in the cost of sickness other than the physician's bill, and the adequacy of the service provided must be considered. The program of studies is a comprehensive one. It deals with questions of supply, demand, distribution and costs of all kinds of services, both preventive and curative, the relation of these costs to other expenses, the return accruing to the practitioners and various agents furnishing medical services, and especially will it seek to determine what standards of adequacy may reasonably be expected.

## II.

Dr Ray Lyman Wilbur, Chairman of the committee, proposed at the meeting May 2nd a statement of three fundamental principles for the consideration of the committee. This statement was referred to each of four subcommittees which held sessions during the two day meeting. The entire committee, at its last session, May 3rd, adopted with a few verbal changes

the three principles. These will be of special interest to the physicians and dentists. They follow:

- 1 *The personal relation between physician and patient must be preserved in any effective system of medical service.*

Medical service is and doubtless, by its very nature, must remain a distinctly personal service. Even in this age of standardized commodities for the table, ready-to-wear clothing, and interchangeable spare parts for all types of machines, there has been no plan suggested for the reduction of medical diagnosis and treatment to basic units which can be ordered from travelling salesmen or acquired through correspondence courses. The physician must see his patient and see him, in many cases, over an extended period of time if the diagnosis and treatment are to achieve the greatest possible accuracy and efficiency. There is no substitute for personal observation.

Man is not a standardized machine and each individual reacts to the conditions of life in a manner in some respects unique. In the treatment of disease, this individual variation is a factor of great significance and can receive due consideration only when the practitioner has known the patient for a considerable time and maintains a personal relation with the patient.

- 2 *The concept of medical service of the community should include a systematic and intensive use of preventive measures in private practice and effective support of preventive measures in public health work.*



The cost of adequate curative treatment is now high and may continue to increase as expensive procedures resulting from scientific progress become more widely used. Sickness, in addition, involves other personal and social costs, some of which cannot be measured in monetary terms.

The outstanding achievements in scientific medicine have been made in the preventive rather than the curative field. Knowledge now available for the control of malaria, tuberculosis, smallpox, diphtheria, pellagra, typhoid fever, hookworm disease, and goiter, if effectively applied, would make unnecessary a considerable proportion of the present expense for the cure of sickness.

3. *The medical service of a community should include the necessary facilities for adequate diagnosis and treatment.*

From the standpoint of effective diagnosis, many diseases, such as tuberculosis, cannot be recognized promptly in their early stages without the aid of elaborate technical equipment. From the standpoint of adequate therapy, if the best of modern technique is not immediately available, complete cures are either delayed or

rendered impossible of attainment. To cite a specific illustration of the improvement of modern therapeutic procedures over those of ten years ago, the time required for treatment of fractures of the hip, and the percentage of permanent invalidity resulting from that injury have each been reduced by more than half.

We cannot be content with anything except the best possible service that modern science can provide and it is therefore imperative that modern scientific equipment for the diagnosis and treatment of disease be available to the practitioners of medicine in every community.

Special Committee of Private Practitioners

Stewart R. Roberts, M.D., Chairman

Walter P. Bowers, M.D.

A. C. Christie, M.D.

Haven Emerson, M.D.

George E. Follansbee, M.D.

M. L. Harris, M.D.

J. Shelton Horsley, M.D.

Kirby S. Howlett, M.D.

Arthur C. Morgan, M.D.

Herbert E. Phillips, D.D.S.

C. E. Rudolph, D.D.S.

Richard M. Smith, M.D.

N. B. Van Etten, M.D.

## Abstracts

### *Outbreak of Psittacosis in a Department Store* By L. F. BADGER (Public Health Reports, June 20, 1930)

Four cases of psittacosis, all employees of a department store employing 500-600 persons, were reported by 3 physicians, 1 physician reporting 2 cases. It was learned on visiting these cases, that a number of other employees were ill at the time with apparently similar symptoms. Most of these were employed on the floor on which parrots were kept. Twenty-five employees were absent from work for periods of four weeks or longer. The onset of their illness occurred between December 14 and January 13. Histories typical of psittacosis were obtained on 17 of the 25. The following are the symptoms of the cases summarized: Rather sudden onset, chills, fever, malaise, severe headache most frequently occipital, loss of appetite, coated tongue, constipation (occasionally diarrhea), unproductive cough, marked bronchitis with indefinite areas suggesting pneumonia, fever reaching 103° or 104° F, lack of definite gastrointestinal symptoms, lung pathology out of proportion to other findings, delirium varying in degree, leucocyte count normal or below. From the manner in which the parrots were handled in the department store there existed abundant opportunity for both direct and indirect infection. The birds were cared for by four of the employees, three of whom became ill. Other employees would frequently visit and handle the birds, particularly was this common during the noon hour. It was probably not rare for customers to come into direct contact with the birds. The opportunity for infection through indirect contact was also great, especially since the parrots were kept on perches outside the cages during the day, and on one occasion had escaped and were free about the floor. Four of the cases, on whom complete histories were obtained from

their physicians, denied any direct contact, 12 admitted direct contact, and in 1, due to death, the mode of contact was undetermined. There were probably many unknown cases occurring among the employees. It was not uncommon for employees from floors other than the one on which the birds were kept to visit and handle the parrots, yet but three cases in such employees are known. One case, terminating fatally, occurred in a non-employee who had visited and fondled the parrots. There existed a possibility that other similar cases occurred. A remarkably high morbidity rate occurred in the employees on the floor on which the birds were kept. The floor is L-shaped, and a section at the end of one wing was reserved for birds. In this wing from 20 to 30 persons were employed, among which 18 of the known 25 cases occurred. Parrots obtained from the same importer as were these implicated in this epidemic have caused cases of psittacosis in other sections of the country. In addition to the parrots, some of the parakeets might have been a factor in the spread of the disease. Approximately 24 parakeets died, and numerous reported cases of psittacosis have been contracted from this bird.

### *The Circulatory Failure of Diphtheria* By FRANCIS F. SCHWENTKER and WILLIAM W. NOEL (Bull. of the Johns Hopkins Hospital, November, 1929, April and June, 1930)

This work is reported under the heads of I, The Clinical Manifestations of Early and Late Failure, II, The Carbohydrate Metabolism in Diphtheria Intoxication; III, The Treatment of the Circulatory Failure of Diphtheria. The first division confirms the studies of Warthin and Marvin in regard to the classification of the circulatory failure of diphtheria into two groups, early and late on the basis of the clinical symp-

toms and the pathological picture presented. Early circulatory failure is an essential part of the diphtheria intoxication and should be treated accordingly. The late circulatory failure, however, is a complication of the disease, caused probably by local inflammatory reactions incident to regeneration and repair. In the second division of the investigation the authors present evidence which points to a marked abnormality in the carbohydrate metabolism in cases of diphtheria intoxication. This is manifested by a primary increase in glycogenolysis in the first stage of the toxemia and a resultant rise in blood sugar. Following this there appears a marked hypoglycemia in very severe cases. In the more protracted cases, however, there seems to follow a decrease in glycogenesis, due probably to a suppression of the production of insulin, with a resultant hyperglycemia. The liver and muscles show a marked diminution in glycogen content in all cases. They feel, therefore, that the symptoms of diphtheria intoxication are in a large part due to secondary nutritional disturbances in all of the essential body tissues. The administration of insulin in these cases causes the assimilation of the dextrose, most probably through the usual glycogenic channels. A consideration of these facts suggests a mode of treatment. If carbohydrates were supplied to the body through intravenous injections of dextrose, and then made available by the administration of insulin, these nutritional disturbances might be balanced. In this way, the toxic patient showing signs of circulatory collapse might receive sufficient support to allow the antitoxin to counteract the toxemia and ward off impending death. They treated 14 cases suffering from diphtheria with intravenous injections of dextrose. All of them were so toxic that death was imminent, several were unconscious. Three of the patients showed no symptoms referable to circulatory embarrassment, four showed a loud systolic murmur. In one case there was an enlarged painful liver but no other signs of a failing circulation. Three patients presented a systolic murmur and an enlarged liver only, in two cases there was an evident cardiac arrhythmia in addition to the murmur and enlarged liver, while in one

patient a systolic murmur, an enlarged liver, an arrhythmic pulse and a protodiastolic gallop rhythm gave evidence of a severely damaged circulatory system. Thirteen of these cases recovered. In most instances the symptoms were rapidly alleviated, the temperature and the pulse rate returned to normal within 24 hours after the injection, the toxic condition disappeared, and convalescence was uneventful. Two of the patients, however, remained toxic for two days despite large doses of antitoxin and frequent intravenous injections of dextrose. From the throat of these patients hemolytic streptococci were cultured in addition to the Klebs-Loeffler bacillus. In one case death occurred four hours after admission. The patient, however, had been ill for days and was moribund when first seen. The authors believe, that, in most of these cases, death would have supervened had the patients not received sufficient dextrose to supply nutrient material to a rapidly failing circulatory system. For this reason, they have adopted in cases of severe toxemia and early circulatory failure in diphtheria, the following general management. The patient receives immediately on admission a large dose of antitoxin intramuscularly. One-half hour later, if no reaction has occurred, 10,000-20,000 units of additional antitoxin and 20 grams of a 50 per cent solution of dextrose are injected intravenously. Ten to twenty units of insulin are supplied intramuscularly. They prefer, in this stage, to supply the fluid by the subcutaneous or intraperitoneal route rather than risk an added load on a failing circulation. Should the patient be restless, which is rarely the case, sedatives are given to obtain complete rest. At intervals varying from 12 to 24 hours, according to the degree of toxemia, the intravenous injection of dextrose is repeated, each time supplemented by insulin. The quantity is so chosen that 1 unit of insulin is given for each 1-2 grams of dextrose. The more toxic the case, the greater the amount of insulin necessary to cause complete utilization of the carbohydrate. After the first or second injection, the dextrose may be given as a 10 per cent solution in order to supply the needed fluid. The administration of dextrose and insulin in

this manner is repeated until the patient's condition is satisfactory and recovery seems certain. There is no rationale in treating cases of late circulatory failure in this manner, since the patient is already in convalescence and the carbohydrate metabolism has returned to normal. It seems, to the writers, however, that the administration of dextrose in the early stages would lessen the degenerative changes in the myocardium, and thus decrease the late inflammatory reaction which is so apt to cause delayed circulatory failure. It may be significant that despite the toxic condition of all the cases treated with dextrose, only two developed any sort of late circulatory abnormality, and these were only transient extrasystoles [This is an important contribution to the therapy of diphtheria, and if these extraordinary results can be confirmed by others, this method of treatment must tend to lessen greatly the mortality in this disease, inasmuch as diphtheria deaths are today chiefly the result of the toxic action upon the myocardium. *Note by editor*]

*A New Meningococcus-like Organism (Neisseria flavescens n. sp.) from Epidemic Meningitis* By SARA BRANHAM (Public Health Reports, April 18, 1930)

During an epidemic of cerebrospinal meningitis in which all four of the usual types of meningococci were involved, an apparently new form was isolated from the spinal fluid of 14 cases. In morphology this microorganism is indistinguishable from the other members of the genus *Neisseria*. It differs from the meningococcus in pigment production, lack of fermentative action, and in antigenic relationship. These 14 strains form a homogenous group culturally, biochemically and serologically. The name, *Neisseria flavescens*, n. sp., is proposed for this new form. Since 30 per cent of the spinal fluid strains received from this locality belong to this group comprising 9 per cent of the total number of strains received at the Hygienic Laboratory during 1928-29, since it is not represented in any of the therapeutic polyvalent serums now manufactured, and since the mortality in these cases was at least 30 per cent, the occurrence of *N. flavescens* in epidemic meningitis warrants especial attention.

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*The Incidence of Bovine Tuberculosis in Children* By R. M. PRICE (Canad. Public Health Jour., 1929)

In a study of tubercle bacilli isolated from children, 190 strains recovered from both medical and surgical cases were identified. Of these, 160 strains proved to be of human variety, and 30 strains, recovered from 20 different patients, proved to be of bovine origin. In the majority of cases from which the human type was recovered, a history of contact to open pulmonary tuberculosis was obtained, and in a certain proportion of the surgical cases there was evidence of tracheobronchial or pulmonary tuberculosis, demonstrable on physical examination or X-ray. All these children reacted to tuberculin. Thirty strains of bovine tubercle bacillus were recovered from twenty patients in our series, the oldest being a patient twelve years of age, and the youngest an infant of five months. In most of the cases investigated, a direct relationship with infected milk was demonstrated. In one of the cases studied, it was possible to demonstrate tubercle bacilli in the milk used. It is of interest to note that the bovine strains isolated were recovered from different sources, namely, cerebro-spinal fluid, meninges, lymph glands, mastoid process, tonsils, adenoid tissue, kidneys, and in one instance from the sputum. Of these regions, the lymph glands, particularly those of the neck, were the most common sites of infection. All these children came from districts in regions where pasteurization of milk was not carried out. In all cases the evidence pointed to an alimentary route of infection. From this limited study it would appear that bovine tuberculosis is a factor in childhood infection in rural Canada, and in unpasteurized areas. The incidence of such infection is probably far greater than we are aware of. Milk is the vehicle for the transmission of the bovine tubercle bacillus. Tissue localization of the bovine tubercle bacillus is peculiar to certain regions, the lungs being practically immune. In the Toronto district, which is a pasteurized district, not a single case of bovine infection has been recovered.

<p>up to the present time. If it is permissible to draw conclusions in terms of percentage incidence from this small group of cases studied, about 12 per cent of surgical tuberculosis in children, leading to operation, dis-</p>	<p>ablement and disfigurement, and occasionally leading even to the death of the child, is preventable, and can be easily controlled by the simple means of pasteurization, or boiling of milk</p>
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## Reviews

*Tuberculosis Among Children* By J ARTHUR MYERS, Ph D, M D, F A C P, Chief of Medical Staff, Lymanhurst School for Tuberculous Children, Associate Professor of Preventive Medicine, University of Minnesota With Chapters by C W Stewart, M D, Ph D, Assistant Professor of Pediatrics, University of Minnesota, Paul W Greisler, M D, Assistant Professor of Orthopedic Surgery, University of Minnesota An Introduction by Allen K. Krause, M D, Director, The Desert Sanatorium and Institute of Research, Editor, American Review of Tuberculosis 208 pages, 43 illustrations, 1 color plate of the Mantoux reaction Charles C Thomas, Springfield, Illinois, 1930 Price in cloth, \$3 50

This work is divided into two parts, the first of which, Tuberculosis in Infancy, consists of eight chapters Congenital Tuberculosis, Exposure to Tuberculosis and Tuberculous Infection, Diagnosis of Tuberculous Infection, Allergy and Immunity, Childhood Type of Tuberculosis in Infancy, Other Forms of Tuberculosis in Infancy, Tuberculous Meningitis, and Prevention of Tuberculosis in Infancy Part II, Tuberculosis in Childhood, has the following chapters Incidence of Tuberculous Infection in Childhood, Tuberculous Lesions in the Chest in Childhood, Tuberculosis of the Bones and Joints, Other Tuberculous Lesions in Childhood, Chronic Non-tuberculous Basal Pulmonary Diseases in Childhood There is much good material in this book, but the reviewer on examining it obtained an impression that it is too condensed Some subjects are too briefly considered In a book on tuberculosis in infancy and in childhood surely more attention should have been accorded the bovine tubercle bacillus than the brief mention given it on pages 61, 63 and 83 Further the discussion on placental tuberculosis and placental transmission is

very superficial, and the conclusion that congenital tuberculosis rarely occurs in the human family is not supported by the actual evidence in the literature Schmorl's work is not mentioned, nor is the evidence from the Pathological Laboratory of the University of Michigan, from which eight cases of placental tuberculosis have been reported in a series of routine examinations of placentas Only the literature on the subject since 1922 has apparently been examined, and not all of that appears to have been known to the writer From the reviewer's standpoint Chapter I is superficial and misleading in its conclusions The author, however, but reiterates the commonly accepted textbook statements as to the frequency and importance of congenital tuberculosis To be commended, however, are his conservative statements regarding the Calmette vaccine, and its possible dangers These have only recently been confirmed in the unfortunate experience in Germany The book is a very good, but very concise, clinical manual of tuberculosis in the early years of life, and for this reason will be worth its purchase and perusal by any one who is engaged in, or interested in, the practice of pediatrics, or of tuberculosis

*Diabetes Directions for Treatment by Insulin and Diet* By BENJAMIN F SMITH, M D, Physician and Lecturer to St. Joseph's Infirmary, Hermann Hospital, and Jefferson Davis Hospital, Houston, Texas 222 pages D Appleton and Company, New York, 1930 Price in cloth, \$2 00

According to the author's preface this little manual has been gradually evolved to meet the needs encountered in the author's practice while caring for diabetes For a time, the diets, etc, were written out for the patients, then mimeographed sheets were used, and finally the demand upon his time

and the number of sheets required for each patient made it necessary to assemble the information in the form of a small book. The feature of the manual is the table of diets so arranged that the carbohydrate content may be changed without changing the protein or caloric value. Such an arrangement greatly facilitates the determination of the patient's tolerance for carbohydrate, a very great help when the patient is treated at home. The diets are composed of simple foods, viz —oatmeal, grapefruit, 5 per cent vegetables, cream, egg, beef, bacon, butter, and, in diets containing larger amounts of carbohydrate, potato and bread. Numerous substitutes for these foods are given and in definite amounts, so that they may readily be included in any meal. Information and instructions are given which enable the patient to cooperate with his physician. The book is divided into seven chapters: General Considerations, Insulin; Instruction to Patients, Classification of Vegetables, Fruits and Fish, Diets, Substitute Foods, and Recipes. Of the making of books of this type, there seems to be no end, as in the last several years we have reviewed at least a dozen of its kind in these columns. The excuse for the appearance of so many manuals for the diabetic would appear to lie in the fact that each successful specialist in the treatment of diabetes, or who has many cases of this disease to treat, comes, sooner or later, to work out a method all his own, differing in various aspects from those followed by other specialists in the same field. Naturally he desires a manual for his own convenience, which will adequately present his own peculiar slant, and which can be used for distribution among his own patients. One would think that there would be an identical sameness in the various manuals that have been published, but this is not the case, as each reflects the individual experience of the author. Perhaps the only way out of it for the general practitioner is to examine them all, and then to choose the one he likes best, or finds best adapted to his own views and practices. The general information concerning diabetes given in these manuals is about the same, and is usually very elementary and adapted to the layman. In this book this material occu-

pies only eighteen pages, the remainder of the book is given over to diets. These appear to be more simple than most of the diet lists offered in manuals of this type; and are less stereotyped and monotonous. They cannot help but be of service to the general practitioner in the planning of special diet programs.

*Normal Facts in Diagnosis* By M. COLEMAN HARRIS, M.D., Lecturer on Physical Diagnosis, New York Homeopathic Medical College and Flower Hospital, New York, and Benjamin Finesilver, M.D., Lecturer on Diseases of the Nervous System, New York Homeopathic Medical College and Flower Hospital. 247 pages, 42 engravings, some in colors. F. A. Davis Company, Philadelphia, 1930. Price in cloth, \$2.50.

This volume has arisen out of the experiences and subsequent convictions of the authors, who believe that no discernment of pathologic signs can be made without a thorough knowledge of the normal. In the usual teaching of Physical Diagnosis pathologic facts are so intermingled with the normal that it is difficult, if not impossible, for the student to differentiate the normal findings. Even the average practitioner is usually inclined to lay stress on abnormal findings, and to lose sight of those signs which occur in the normal individual. There are nine chapters which consider the normal temperature, pulse, respiration, height, weight, to head and neck, chest, abdomen, the extremities, pelvic and rectal examinations, and the sensorimotor examination, with laboratory findings, and a final chapter on senescence. The material used in this book seems to be correct and well chosen. The chief criticism is its incompleteness. There are many important omissions. Any modern study of the normal facts in diagnosis should certainly include the description of the chief constitutions, with their anatomic and physiologic differences. There is no generic conception of the normal, a point which this little volume does not emphasize as it should. In this respect its statements as to what is normal are too dogmatic. The inadequacy of the material is shown in the chapter on Senescence,

which comprises a bare two pages full of matter

*Physical Diagnosis* By RICHARD CABOT, M.D., Professor of Clinical Medicine in Harvard University, Formerly Chief of the West Medical Service at the Massachusetts General Hospital Tenth Edition. Revised and enlarged, with 529 pages, six plates and 279 figures in the text William Wood and Company, New York, 1930 Price in cloth, \$5.00

This well-known work on physical diagnosis has now reached its tenth edition, sufficient evidence of its value to the student and to the practitioner. Written with a strong individual slant, amounting in some instances to personal bias, this work is highly suggestive and stimulating to the student of medicine. It endeavors to present an account of the diagnostic methods and processes needed by competent practitioners of the present date. It differs from other books on the subject "in that it makes no

attempt to describe technical processes with which the writer has no personal familiarity, and gives no space to the description of tests which he believes to be useless." The author herein sounds his declaration of independence, and bases his work upon his individual experience. "All that I have described I know by prolonged use." As he himself acknowledges, a book constructed on this basis should make obvious what its writer considers important and what unimportant, and reveal therein not only his opinions but his personal limitations as well. This book does both of these things, and the author's method is at the same time the source both of his strength and of his deficiencies. The work is consequently extremely dogmatic, even to the degree of cocksureness, but it nevertheless is a book that is of very great value, as it has proved itself to be through the years. This new edition contains important new matter relating to coronary disease, electrocardiography, cancer of the lung, "cardiac asthma," toxic hepatitis and encephalitis lethargica.



## College News Notes

Dr Harry M Hall (Fellow), Wheeling, W Va, addressed the Seventh Councilor District Medical Society of Pennsylvania on June 13 at Philadelphia, his title being, "Should we Lead or Follow."

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Dr Orlando H Petty (Fellow), Philadelphia, Pa, addressed the Eleventh Councilor District Medical Society, June 12, on "Management of Some Complications of Diabetes"

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Dr Seale Harris (Fellow), Birmingham, Ala, delivered a paper on "Home Treatment of Diabetes" before the East Tennessee Medical Association at Kingsport, May 9

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Dr James B Herrick (Fellow), Chicago, Illinois, was awarded the Kober Medal of the Association of American Physicians at the Meeting in Atlantic City, May 6, 1930 This medal is awarded annually for notable work in preventive medicine

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On the programme of the American Association of Physicians at the Atlantic City Meeting, May 6 and 7, were Dr J B. Herrick (Fellow), Dr. Cyrus B Sturgis (Fellow), Dr A S Warthin (Master), Dr Lewis A Conner (Fellow), Dr C. V. Weller (Fellow), and others of the College

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Dr A Morris Ginsberg (Fellow), Kansas City, Mo, recently contributed the following reprints of his publications to the College Library.

'Hemoptysis in Mitral Stenosis"

"Hemochromatosis" (With Paul M Kroll)

'Clinical Significance of Precordial Pain" (With Arthur C. Clasen)

'Splenomegaly" (With Arthur C Clasen)

In the May Issue of the Journal of the Oklahoma State Medical Association, the following papers were contributed by Fellows of the College as indicated

"Objective Findings in Heart Disease Without Failure," by Russell C. Pigford, Tulsa, Okla.

"The Laboratory As An Aid in the Diagnosis of Syphilis," by T C Terrell, Fort Worth, Texas

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Dr Herman M Baker (Fellow), Evansville, Ind, was a visitor at the College headquarters on May 26

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Dr. William Gerry Morgan (Fellow), Washington, D C, was inducted President of the American Medical Association at its opening session in the Masonic Temple, Detroit, on June 24

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Dr Thomas P. Murdock (Fellow), Meriden, Conn, has succeeded Dr Robert L Rowley, of Hartford (resigned), as Secretary of the Connecticut Medical Examining Board

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Dr John R Vonachen (Fellow), Peoria, addressed the Morgan County (Illinois) Medical Society at Jacksonville, May 8, on "Urologic Conditions in Infancy and Childhood"

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Dr. Martin L. Stevens (Fellow), Asheville, was elected President-Elect of the Medical Society of the State of North Carolina at its meeting at Pinehurst, April 28-30 Dr L. B. McBrayer (Fellow), Southern Pines, was re-elected Secretary The next annual session of the Society will be held, April 20-22, 1931, at Durham

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Dr Frederic J Farnell (Fellow and Governor of the College for the State of Rhode Island has been appointed by Hon Norman

S Case, Governor of the State of Rhode Island, as Chairman of the Public Welfare Commission of that state, official representative of Rhode Island to the Tenth International Prison Congress, to be held in Prague, Czecho Slovakia, August 25-30, 1930

Lr Beverly R Tucker (Fellow), Richmond, Va, has presented an autographed copy of his late book, "The Gift of Genius," to the Library of the American College of Physicians

Dr Philipp Schonwald (Fellow), Seattle, Washington, presented the following reprints of his publications to the College, recently

"Clinical Aspects of Bronchial Asthma and Hay Fever"

"Institutional Theatment of Tuberculosis"

"Zur Behandlung der Mischinfektion bei Tuberkulose"

Dr Hyman I Goldstein (Associate), Camden, N J, spent six months in postgraduate work and visiting clinics in Vienna, Prague, Budapest, Leipzig and Paris last summer and winter

Dr Goldstein read a paper on "Recent Advances in Diagnosis and Treatment" before the Camden County Medical Society at its May meeting. He also presented a paper on "Hereditary Epistaxis (Familial) with or without Hemorrhagic Multiple (Hereditary) Telangiectasia" before the State Medical Society of New Jersey at its 164th annual meeting at Atlantic City on June 13

Dr H Harlow Brooks (Fellow), New York, received an Honorary Degree of Master of Science, from the University of Michigan, June 23, 1930

Dr Daniel N Silverman (Fellow) was a speaker at the first joint meeting of the Fifth District Medical Society, Louisiana, and Tri-County Medical Society, Vicksburg, Miss. His subject was "Experiences with the Peptic Ulcer Problem"

Dr George R Minot (Fellow) and Dr William P Murphy, of Boston, were awarded the Cameron Prize of the University of

Edinburgh, Edinburgh, Scotland, in recognition of their work concerning the beneficial effect of liver therapy for patients with pernicious anemia

On May 8, 1930, Dr Minot was awarded in New York City, the gold medal of the National Institute of Social Sciences

Dr Soma Weiss (Fellow), Boston, is on leave of absence to make a survey of numerous medical clinics in central Europe

Dr H L Ulrich (Fellow), Minneapolis, used as his title "Report of three cases of Coarctation of the Aorta" in his Presidential address before the Minnesota Pathological Society at the University of Minnesota Medical School, Institute of Anatomy, on May 20

Dr John E Legge (Fellow), Baltimore, delivered an address on "A Useful Sign in the Diagnosis of Ureteral Stricture and Its Sequelae" at the meeting of the Grant-Hardy-Hampshire-Mineral Medical Society at Piedmont, W Va, on April 19

Dr John M McCants (Fellow), Lieutenant-Commander, M C, U S N, has been transferred from the U S S Relief at San Francisco to the U S Naval Medical School at Washington, D C, where he will teach and have charge of the Bacteriological Laboratory

Drs Joseph C Doane (Fellow) and Henry B Wilmer (Fellow), Philadelphia, were elected Directors of the Philadelphia County Medical Society at its business meeting on May 21

Dr S Calvin Smith (Fellow), Philadelphia, was elected Vice President.

Dr Herbert Bryans (Associate), Pensacola, Florida, was Chairman of the Entertainment Committee for the 57th annual meeting of the Florida Medical Association held at Pensacola during early May

Dr George Blumer (Fellow), of the Yale University Medical School, made rounds and gave clinics at the Penobscot County Medical Society at Bangor, Maine, May 19-20

Dr Abraham E Jaffin (Fellow), Jersey City, N.J., during 1929 was appointed Attending Physician to Christ Hospital, Chief Attending Physician to the Hudson County Tuberculosis Clinics, Official Delegate from the National Tuberculosis Association to the International Union Against Tuberculosis meeting at Oslo, August 13-15, 1930 Dr Jaffin will spend some time doing post-graduate work in cardiology and tuberculosis at Vienna during his trip abroad

Dr Henry I Klopp (Fellow), Allentown, Pa., spoke on "The Development of a Children's Institution for Mental Health," at the meeting of the Philadelphia Psychiatric Society on May 16, at Philadelphia College of Physicians

Dr. Carl V Vischer (Fellow), Philadelphia, is co-author of an article, "The Use of Mono-Iodo-Cinchopen in the Treatment of Chronic Arthritis" This is a report of the "Arthritis Conference" of Hahnemann Hospital and was the contributed article in the May issue of the Hahnemannian Monthly

Dr. W D Sansum (Fellow), Santa Barbara, Calif., Director, Potter Metabolic Clinic, Santa Barbara Cottage Hospital, is author of "The Normal Diet," a simple statement of the fundamental principles of diet for the mutual use of physicians and patients This is the third revised edition of this successful book

Dr J. M McCants (Fellow), Lieutenant Commander, M.C., U.S.N., assumed charge of the bacteriological and serological laboratories of the U. S. Naval Medical School at Washington, D.C., on May 16, 1930 He also became instructor in bacteriology and serology at the Naval Medical School

Dr R. R Gasser (Fellow), Lieutenant Commander, M.C., U.S.N., has been detached from duty at the Naval Medical School, Washington, D.C., and ordered to duty as Medical Officer of the U. S. S. Northampton The U. S. S. Northampton is one of the largest hospital cruises of the U. S. Navy

Among members of the Special Committee of Private Practitioners, who are also members of the Committee on the Costs of Medical Care, are the following

Dr. Stewart R Roberts (Fellow), Chairman, Atlanta, Ga

Dr A C Christie (Fellow), Washington, D.C

Dr Arthur C Morgan (Fellow), Philadelphia, Pa

As Chairman of the Committee, Dr. Roberts has recently distributed a report on "The Scope and Aim of the Committee on the Cost of Medical Care"

Dr Harold L Barnes (Fellow), Brooklyn, N.Y., is the author of a paper on "Soft Curd Certified Milk" in the May Issue of the Long Island Medical Journal

Dr Horace W Soper (Fellow), St Louis, Mo., is the author of a paper on "Diathermy of the Rectum and Pelvic Colon" in the June Issue of the Journal of the Missouri State Medical Association

Dr W McKim Marriott (Fellow), St Louis, Mo., Dean of Washington University School of Medicine, was a speaker at the 65th annual convention of the Missouri State Dental Association at St. Louis, May 19-22.

Dr Lewis A Conner (Fellow), New York, N.Y., Professor of Medicine, Cornell University Medical College, used as his subject "The Place of Laboratory Aids in the Practice of Medicine and Surgery" in an address on May 20 before the St Louis Medical Society

Dr Conner is one of the founders and first president of the American Heart Association, and Editor of the American Heart Journal

Dr. Morgan Smith (Fellow), Little Rock, Ark., has been elected a member of the Pulaski County Board of Education

Under the Presidency of Dr William A. White (Fellow), Washington, D.C., the International Congress on Mental Hygiene held its sessions there, May 3-10

Dr Carl V Vischer (Fellow), Philadelphia, Pa, is the author of an article, "Management of Pulmonary Hemorrhage in Tuberculosis," which appeared in the May number of the Hahnemannian Monthly

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Dr Paul D White (Fellow), Boston, Mass, is author of an article entitled "The Prevention of Heart Disease," appearing in the June Issue of the Virginia Medical Monthly

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Dr. Frank N Allan (Fellow), Rochester, Minn, addressed the New Mexico Medical Society's annual meeting, June 4-6, on "Treatment of Diabetes"

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Dr Kenneth M Lynch (Fellow), Charleston, S C, was elected President of the South Carolina State Medical Association during its annual meeting held at Florence, S C, recently

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Dr Chester W Waggoner (Fellow), Toledo, Ohio, was installed as President of the Ohio State Medical Association at Columbus on May 15

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Dr Edgar A Hines (Fellow), Seneca, S C, has been re-elected Secretary of the South Carolina Medical Association

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Dr James H Means (Fellow), Boston, Mass, has been re-elected Secretary of the Association of American Physicians

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Dr Cyrus C Sturgis (Fellow), Ann Arbor, Mich, has been re-elected Secretary of the American Society for Clinical Investigation

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Dr Charles G Lucas (Fellow), Louisville, Ky, has been re-elected Secretary of the American Gastro-Enterological Association

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Dr Allen H Bunce (Fellow), Atlanta, Ga, has been re-elected Secretary of the Medical Association of Georgia

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Dr George Morris Piersol (Fellow and Secretary-General of the College), Philadelphia, Pa, was installed as President of the

American Climatological and Clinical Association, at Quebec, Canada, May 13

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Dr Felix J Underwood (Fellow), Jackson, Miss, and Dr George W McCoy (Fellow), Washington, D C, addressed the joint session of the State and Provincial Health Authorities of North America and the State and Territorial Health Officers of the United State Public Health Service at Washington, D C, June 18-20, on the subjects, "County Health Work Appraisal on Basis of Morbidity and Mortality" and "Antirabic Paralysis Consideration of Various Vaccines," respectively

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Dr James B Herrick (Fellow), Chicago, Ill, was among those giving special clinics to Rush Medical College Alumni during the Commencement Week of the Chicago University

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Dr Walter C Alvarez (Fellow), Rochester, Minn, and Dr Clarence R Strickland (Fellow), Indianapolis, Ind, were among the speakers at the Ninth District Medical Society's meeting at Noblesville, Ind, on May 15

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Dr Ray M Balyeat (Fellow), Oklahoma City, Okla, addressed the Bourbon (Kansas) County Medical Society, April 29, on "Allergy"

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Dr Aaron E Parsonnet (Fellow), Newark, N J, addressed the Middlesex County Medical Society, April 16, on "Coronary Thrombosis"

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Dr Carl J Wiggers (Fellow), Cleveland, Ohio, will deliver the Beaumont lecture at the Physicians Hospital of Plattsburg, N Y, August 22-2, Dr Wiggers' title being, "Physiologic Meaning of Common Clinical Signs and Symptoms in Cardiovascular Disease"

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Dr William E Robertson (Fellow), Philadelphia, Pa, and Dr Edward C Reifstein (Fellow), Syracuse, N Y, will also deliver papers during the sessions

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Dr David Marine (Fellow), New York, N Y, recently addressed the New York

Physicians' Association on "Pathologic Physiology of Graves' Disease"

Dr. Henry T. Smith (Fellow), McGehee, Ark, addressed the Desha County Medical Society, April 22, on "X-Ray Findings in Negro School Children"

Dr. William Gerry Morgan (Fellow), Washington, D C, President of the American Medical Association, received the degree of Doctor of Laws from the Georgetown University, and the degree of Doctor of Science from Dartmouth College, during June

Dr Allen H. Bunce (Fellow), Atlanta, Ga, addressed the Fourth District Medical Society of Georgia, recently, on "Carcinoma of the Colon."

Dr Henry C Sauls (Fellow), Atlanta, Ga, delivered an address on "Heart Disease" before the Spalding County (Ga.) Medical Society on April 16

Dr Sidney A. Portis (Fellow), Chicago, Ill, Professor of Medicine at the Loyola University School of Medicine, conducted a medical clinic at St Mary's Hospital at Quincy, Ill, May 12, in connection with the meeting of the Adams County Medical Society

Dr Estes Nichols (Fellow), Portland, Maine, delivered a paper on "Treatment of Tuberculosis" before the Kennebec County Medical Association of Maine at Gardiner on April 22.

Dr John E. Grewe (Fellow), Cincinnati, Ohio, addressed the Highland County and Five County Medical Societies, recently, on "Hypertension with Some Newer Phases of the Circulation."

Dr Harry M. Hall (Fellow), Wheeling, W. Va., delivered a paper recently before the Licking County (Ohio) Medical Society on "Speech"

Dr Laurence Sefton (Fellow), Portland, Ore, is Vice President of the Portland Child Guidance Clinic Association recently organized

Dr Daniel J McCarthy (Fellow), Philadelphia, Pa, read a paper, May 8, at Johnstown, before the Cambria County Medical Society on "Arteriosclerosis and Its Effects on the Central Nervous System"

Dr. Henry K. Mohler (Fellow), Philadelphia, Pa, spoke on "Diabetes Mellitus," May 7, before the Montgomery County (Pa) Medical Society.

Dr Martin L. Bonar (Fellow), Morgantown, W. Va, addressed the Monongahela County Medical Society, May 6, on "Treatment of Skin Diseases"

Dr John H. Musser (Fellow), Professor of Medicine at Tulane University of Louisiana School of Medicine, delivered a course of lectures and clinics in connection with an extensive graduate medical course in Internal Medicine during the latter part of June and July at Beaven Dam, Beloit, Fond Du Lac, Jamesville, Madison and Watertown. This course is offered under the auspices of the University of Wisconsin Extension Division

Dr. Julius Friedenwald (Fellow), Baltimore, Md, is one of the trustees of the Institute for Advanced Study, which is to be established at Newark, N. J., for graduate work in scientific research. "It will train advanced students for and beyond the degrees of Doctor of Philosophy or other professional degrees of equal standing." It has been reported that Louis Bamberger, Newark, N. J., and his sister, Mrs Felix Fuld, have contributed a fund of \$5,000,000 for the new foundation. Dr. Abraham Flexner, who was formerly the Director of the Division of Medical Education of the General Education Board, is said to have accepted the Directorship of the new Institute

Among Fellows of the College who visited the Executive Offices of the College during June, were:

Dr. Verne Cavins, Raleigh, N. C.  
Dr. Julius Connor, York, Pa  
Dr. Homer Donald, Dallas, Texas  
Dr. Alvin Sevel, Philadelphia, Pa

Dr George E Pfahler (Fellow), Philadelphia, discussed cancer of the uterus during the program of a cancer course held at Harrisburg, June 4, under the auspices of the Dauphin County Medical Society

Dr. Jesse L. Lenker (Fellow), Harrisburg, was a speaker at the symposium on thyroid diseases held before the Dauphin County Medical Society, recently.

Under the Presidency of Dr Ellen C Potter (Fellow), Trenton, N J, the Medical Women's National Association held its annual meeting at Detroit, June 22-24

Dr J W Torbett of Marlin, Texas (Fellow), read an article on "The Classification, Diagnosis and Treatment of Arthritis" at the trecent meeting of the Texas State Medical Association at Mineral Wells. He also received the degree of LL.D at Southern Methodist University at Dallas on the 3rd of June at their regular annual commencement exercises

Dr W Stanley Curtis (Fellow) delivered an address on "The Treatment of Diabetes" at the meeting of the Dallas Southern Clinical Society, held in Dallas on April 14

Dr W B Yegge (Fellow) discussed the subject of "Post-operative Pneumonia versus Atelectasis," from the internist's point of view, at the meeting of the Northeast Colorado Medical Society, at Sterling, Colorado, May 7

The Dallas Southern Clinical Society held its five day conference at Dalas, April 14-18, with a registration exceeding one thousand. Doctors Logan Clendening, Kansas City, Mo, Francis M Pottenger, Monrovia, Cyrus C Sturgis, Ann Arbor, and Alexander B. Moore, Rochester, Minn, were among the guest speakers

Dr Gilbert E Brereton (Fellow), Dallas, was elected Secretary

Dr James Allison Hodges (Fellow), Richmond, addressed the Mecklenburg County (Virginia) Medical Society, April 15, on "Neuropsychic Cases"

Dr Karl E Kassowitz (Fellow), Milwaukee, has been made Associate Professor of Clinical Medicine at the Marquette University, School of Medicine

Dr John E Gonce, Jr (Fellow) and Dr Ray C Blankinship (Fellow), both of Madison, participated in a symposium on jaundice before the Dane County (Wisconsin) Medical Society at Madison, April 15.

Dr Merle Q Howard (Fellow), Wauwatosa, addressed the Milwaukee Academy of Medicine and the Milwaukee Neuro-Psychiatric Society on Pellagra, May 13

Dr William R Bathurst (Fellow), Little Rock, was re-elected Secretary of the Arkansas Medical Society at its meeting at Fort Smith, May 6-8

Dr William Henry Robey (Fellow) and Dr Samuel A Levine (Fellow), both of Boston, have been made Clinical Professor of Medicine and Assistant Professor of Medicine, respectively, at Harvard Medical School, their appointments to date from September 1

Dr Colonel B Burr (Fellow), Flint, Mich, has written the first volume of a two volume Medical History of Michigan, which was distributed on May 15

Dr Albert A Getman (Fellow), Syracuse, N Y, has become a Life Member of the American College of Physicians through subscription to the Life Membership Fund. The Endowment Fund of the College, which thus far has been made up wholly of Life Membership subscriptions, becomes a permanent trust fund of the College, the principal of which must be held intact, while the income only may be used. The Board of Regents has rather adopted the policy that the Endowment Fund shall furnish the source for the promotion of research and writing in the field of Internal Medicine, as well as for other worthy activities the College may find desirable to encourage. The John Phillips Memorial Prize, announced elsewhere in the ANNALS OF INTERNAL MEDICINE, was established from income from the Endowment Fund

Dr Carl V. Vischer (Fellow), Philadelphia, Pa., has contributed the following publications to the Library of the American College of Physicians

"The Use of Mono-Iodo-Cinchophen in the Treatment of Chronic Arthritis"

"Management of Pulmonary Hemorrhage in Tuberculosis"

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Dr Beverley R Tucker (Fellow), Richmond, Va., has contributed a copy of "The Lost Lenore," a one-act play, psychological in character, based on an incident in Edgar Allan Poe's life, to the College Library.

Dr Tucker published during May, through the Stratford Company of Boston, a book entitled "The Gift of Genius," analyzing nineteen geniuses and giving ten chapters on genius

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Dr. W. Stanley Curtis (Fellow), Boston, Mass., presented a paper on "The Treatment of Diabetes" and conducted some hospital clinics at the Dallas Southern Clinical Society's meeting at Dallas during April.

held a dinner and meeting at the Baltimore Club for the purpose of organizing advanced plans for the Fifteenth Annual Clinical Session of the American College of Physicians to be held at Baltimore, March 23-27, 1931. Among those present, in addition to Doctors Miller and Pincoffs, were Dr. Winford Smith, Dr Warfield Longcope, Dr Lewellys F Barker, Dr William Wilmer, Dr Alan Chesney, Dr William Ford and Dr. McCollum. Many plans and ideas for the Clinical Session were presented and discussed. More definite details and specific plans will be announced in later issues.

The Lord Baltimore Hotel will be the general headquarters hotel, but the general sessions, registration, exhibits, etc., will be held in The Alcazar at Cathedral and Madison Sts. The Alcazar furnishes excellent facilities for every phase of the meeting. In fact, The Alcazar is operated more or less as a club hotel, and can accommodate approximately two hundred of our members with single or double rooms. It has an attractive dining room, where our members

# In Defense of the Stethoscope\*

By JAMES B HERRICK, *Chicago*

THERE is a tendency nowadays to attack the stethoscope. It is criticized in print, in addresses in medical societies and in conversation between doctors. As a result it is losing caste as an instrument of diagnosis. Moreover, its loss of prestige carries with it a lessened appreciation of physical diagnosis in general, once a most highly regarded feature in medicine.

The charges against the stethoscope are two: that it is antiquated, its place taken by other methods especially by the x-ray, and that it does more harm than good because its findings are so often misinterpreted.

As to the first charge that it has been, and should be, displaced by the x-ray and other methods of diagnosis —

For diagnosis we must rely as heretofore upon the history and physical examination, with free recourse to instruments of precision, the laboratory, the therapeutic test, or even the exploratory surgical procedure. In this complex of diagnostic agencies the stethoscope and physical diagnosis have a part that is decidedly non-negligible, though we must recognize the fact that the relative values of

these different methods have undergone many changes. Thus in tuberculosis the stress formerly laid on personal and family history and physical examination has been largely transferred to the examination of sputum and the study of x-ray films. The Wassermann test and x-ray have assumed prominent rôles in the recognition of thoracic aneurysm. The x-ray may show a tuberculous focus or an aneurysm that has been missed by the other methods, or it may be decisive in determining the extent of such lesions.

There is however, another side to this question. The stethoscope may discover disease that escapes the x-ray. A few râles at an apex associated with a cough, slight temperature and expectoration may be more convincing than the film that shows no lesion or only suggests it. A pleural or pericardial friction or a diastolic murmur may furnish unmistakable evidence of organic disease that is not shown by x-ray. No x-ray film or even fluoroscopic examination can convey the sense of strength or weakness that is revealed when the trained hand palpates the region of the laboring heart or the stethoscope detects the murmur at apex or base and brings out the character of the closing sounds of aortic and pulmonary

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\*Read before the American College of Physicians, February 12, 1930, Minneapolis, Minn.



valves The x-ray discloses the size and shape of the heart, but not its behavior in action, at least as regards sound and strength To see a photograph of a tired horse stumblingly hauling a heavy load up a hill gives evidence as to the efficiency of the horse In addition, to hear him puff and wheeze, to hear the wagon creak and the driver's whip crack yields important information as to the ability of the horse to carry the load to its destination

Now it can be made earlier by instrumental and laboratory aid We should not allow the stethoscope and all it stands for to go into the discard because forsooth much of the information may be gained by other lazier and supposedly more exact methods We should not teach our students, undergraduate and graduate, that the first thing to do in diagnosis is to rush to the x-ray and electrocardiograph any more than we should teach them that the first thing to do in an abdominal pain is to explore the abdomen surgically This is shirking duty and responsibility and at times leads to grievous error

We should remember, too, that the interpretation of an electrocardiogram, an x-ray film, a laboratory color reaction, a bit of tissue under the microscope—all these interpretations depend on the action of a human brain. That brain may be in error in the laboratory as well as when connected with the earpieces of a stethoscope The optic nerve may err as well as the auditory Also, it is to be noted that properly to put together the results of tests made by different men and different instruments of varying reliability is not an easy task. Strange and unworkable assembled diagnoses sometimes result For truth has a tricky way of slipping out of hand or getting distorted as it is passed from one individual to another. The more remote from the physician the instrument or laboratory, the more the danger of error The stethoscope will be one means of keeping them close to the patient and thus close to the truth Furthermore, it

helps him to retain that important something called the personal touch

The second objection to the stethoscope is that because its findings are so often misinterpreted it does more harm than good

Again we must admit justice in the criticism. A few râles with a roughened expiratory tone, or a murmur at the apex of the heart, and the uninformed or impulsive doctor, or the over-conscientious doctor who feels that in the interest of his patient he must recognize heart disease or tuberculosis in the incipient or hopeful stage, makes a diagnosis of tuberculosis or heart disease with all the penalties thereunto appertaining—psychic upset, altered modes of living and change in occupation. On the basis of the one finding, with disregard of other features, he has jumped to a disastrous conclusion that may be wrong. No wonder the critics cry, "Away with the stethoscope"

Now the same argument may be used against almost any other aid to diagnosis, the clinical thermometer, the sphygmomanometer, the Wassermann test, the reaction for albumin in the urine, the leucocyte count, the facts in a history. Are not their results misinterpreted again and again? Some physicians have said the Wassermann reaction was a curse, for at times positive when there was no syphilis, oftener negative when syphilis exists, it has led to many errors. Others have rebelled against the emphasis laid on casts and albumin in the urine. That blood pressure—too high or too low—is made too much of by the laity and many doctors is well known. And the sins committed

in getting histories, not alone sins of omission but of commission as well, the wrong interpretation of headache, vomiting, dyspnea, cough! One has no difficulty in making a long list of misinterpretations along these various lines. Why, then, should the stethoscope be the instrument singled out as the criminal whose sentence is to be banishment when others are also guilty, at times even more guilty?

The greatest outcry against the stethoscope has come from those who deplore the fact that the murmur revealed by this instrument so often means nothing pathologic yet is regarded by the injudicious examiner as an indication of disease. I will not labor the trite statements about the so-called accidental murmur and the theories as to its origin. If there is no history of rheumatism, if the heart is not large, if the second tones are normal, if there are no symptoms of cardiac incompetence such as dyspnea, cyanosis or râles, and if the murmur is systolic, we are told to let it pass as not meaning organic heart disease. But suppose it is due to anemia, or fever, or cardiac irritability as in exophthalmic goiter, should it not be noted as a symptom of such condition? Should we in cowardly fashion decline to listen for it or to admit its presence or discuss its significance for fear we may misinterpret it? It is up to us to decide whether it means nothing or something. The fault is in us and not in the stethoscope. We should discard our error and not the instrument.

There is another side to the question of the systolic heart murmur. Let us admit that its importance as

an indication of heart disease has been, and still is in many quarters, overstressed. Yet who among us does not in practice value highly the information afforded by murmurs, including those heard in systole? All agree that diastolic murmurs are of great significance as indicating organic disease. We must also insist that many systolic murmurs command our respectful attention because they mean something.

I am inclined to think there is developing a tendency to underestimate the importance of the systolic murmur as an evidence of heart disease. Other signs, such as increase in size of the heart, altered second tones may be trivial or absent. The heart may for the time be competent so that there is no dyspnea. Yet organic disease, such as syphilitic or rheumatic, may lurk in the valves or myocardium. The murmur rightly interpreted may lead to more thorough investigation of the case. A word of caution—not a note of alarm—may be given and the patient saved from a later breakdown. Not a few young men were admitted to active service in the Great War, in spite of a known systolic murmur which was regarded as meaningless.

Some of these young men came out of the army fatally wrecked because of cardiac breakdown.

One other point. Granting that the murmur is by no means the sole criterion of a disease of the heart or of a heart's efficiency, it is worth something in a negative way to examine and find no murmur. It may be a comforting bit of evidence that the heart is all right. We do not exclude tuberculosis because the thermometer, the sputum examination or the x-ray fail to show change from the normal, but we rightly give these negative findings weight in trying to reach a decision. Similarly the stethoscope has a function to perform in excluding the presence of murmurs.

To conclude, this is a plea for the sane use of every means that may help in diagnosis, including the stethoscope and all that it stands for in the way of physical diagnosis. Physical examination should not yet be regarded as displaced by other methods. It still has a legitimate function. Undergraduates and practitioners should still be taught its theory and its practice so that it may not become a lost art.

# The Use of Iodine in Exophthalmic Goiter\*

By J H MEANS, M D , F A C P , *Boston*

AS a result of studies on the action of iodine in exophthalmic goiter begun in the spring of 1923, when Plummer first described its characteristic effect, and continued ever since, we have come to certain conclusions about indications for treatment which seem sufficiently definite to warrant review. What iodine does has become clear, how it does it remains a mystery.

The most characteristic phenomena which this element or its salts produces in persons suffering from real Graves' disease are the rapid amelioration of symptoms, especially the nervous, and the fall in pulse rate and basal metabolic rate which occurs, with but few exceptions, when adequate dosage is employed in patients who are not already under its influence. We have come to look upon this response as one of the earmarks of the disease, and when it fails to occur, at least in some measure, we doubt whether we are dealing with thyrotoxicosis of the true exophthalmic goiter type. It is a therapeutic response as rapid and as specific as that of myxedema to thyroid, perni-

cious anemia to liver extract, or scurvy to orange juice.

The rate at which and the extent to which the intoxication is ameliorated depends in part at least upon the intensity of the latter before iodine is given, and also upon the geographic area in which the case originates. The nervous symptoms may show improvement within a matter of hours, and the metabolism, as we find it in Boston, a non-goitrous region, drops about five points a day in the severely toxic and about three points a day in the moderately toxic patients, the full effect being reached in from eight to ten days<sup>1</sup>. In other words, the farther the state of the subject is removed from normal, the greater is the effect of the corrective agent. This principle applies to many things in medicine. An agent may have little or no effect in the normal and a great one in the diseased. That the characteristic iodine response may be regarded as specific in exophthalmic goiter is indicated by the fact that iodine has no effect on hyperthyroidism induced in man or animals by thyroid feeding<sup>2,3,4</sup> and an uncertain or absent one in what may be taken to be pure adenomatous goiter with hyperfunction.

The matter of locality in relation to the iodine response is of great importance. The severity of the disease

\*From the Thyroid Clinic of the Massachusetts General Hospital.

†Read at the Minneapolis Meeting of the American College of Physicians, February 12, 1930.

is unquestionably greater in goitrous than in non-goitrous regions<sup>6</sup> This is shown by the higher operative death rate in the days before iodine preparation, the greater frequency of toxic crises, and, as recently shown by Collier<sup>7</sup>, the less striking response to iodine in cases arising in goitrous areas When one uses iodine in exophthalmic goiter these geographic differences must always be borne in mind They are, however, differences in intensity or degree, I believe, rather than in kind, the same relations hold in regard to the action of the drug in the goitrous as in the non-goitrous portions of the globe, but in the former the extent and rapidity of its action are likely to be less

Certain other facts about the characteristic iodine response deserve emphasis For one thing, it is important to recognize that the response may be

is in spite of, not because of the drug I have never seen patients with exophthalmic goiter made worse by iodine, nor have I ever been completely convinced that they truly become intolerant or refractory to it The action of iodine in exophthalmic goiter bears some crude analogy to that of digitalis in heart disease or salicylates in rheumatic infection These drugs diminish the intensity of symptoms but do not alter the progress of the diseases in which they are used

The dosage of iodine necessary to bring about the characteristic response is a matter of some interest It, like the severity of the disease, very likely varies from place to place, being greater perhaps in goitrous than in non-goitrous regions The matter has been studied in our Thyroid Clinic<sup>7</sup> and it was found that in twelve out

in acute thyrotoxic crises, it may be larger. We do not know about this having never dared to give the smaller doses to patients of this type. I mention this matter of the minimum effective dose as a point of scientific interest. I do not wish to be understood as recommending such a dose in the routine treatment of the disease. In contrast to digitalis and salicylate, the difference between the dose of iodine that will have full pharmacologic effect in exophthalmic goiter and the toxic dose is very great. There is hardly any danger of giving too much, therefore, we must be sure not to err on the side of not giving enough. We commonly use doses of five, ten or even fifteen minims three times a day, and in a very toxic case we might give more. The much larger doses sometimes used by Plummer<sup>6</sup> we have not found necessary, but this may be because the disease is commonly more severe in his locality than in ours.

Another question of both theoretical and practical interest is that of whether the chemical state of the iodine administered, or the route by which it enters the body, in any way modifies its effect. From such observations as we have made, the answer would seem negative in each case. Potassium iodide solution containing no free iodine acts just like Lugol's solution; ethyl iodide administered via the lungs produces the same result as Lugol's solution or potassium iodide by mouth.<sup>8</sup>

In view of the various considerations based upon the experience we have had, it seems to us working in the Thyroid Clinic of the Massa-

chusetts General Hospital, that the uses of iodine in exophthalmic goiter may be defined fairly categorically. They seem to us threefold.

First and most important, to prepare patients for operation,

Second, to control residual symptoms after operation, and

Third, as a treatment per se of the disease, in certain selected cases.

Of the first use I need say but little, it is familiar to the profession. One takes it for granted nowadays that the way to treat exophthalmic goiter is to get the full effect of iodine and then do an extensive surgical resection of the thyroid gland at once, continuing the iodine meanwhile. Under such management the risk is slight and the postoperative storm is rare. A single warning, however, may not be amiss. In the relatively few cases where the thyrotoxic manifestations show no sign of diminishing under iodine, and especially in those in which they actually increase, operation should be postponed, patients in this phase may die postoperatively, iodine or no.

The second use, that is to control the postoperative residual thyrotoxic manifestations, is of considerable interest and should be known to the physician. Many patients, either directly or a few weeks after subtotal thyroidectomy, and still more often after less extensive resection, show definite symptoms and signs of residual thyrotoxicosis, perhaps with an elevated, but often with a normal metabolic rate. Nearly always these will disappear on small doses of iodine (Lugol's solution one to three minims per day), and with their disappear-

ance pulse and metabolism drop, the latter perhaps to a definitely substandard rate<sup>9, 10</sup> Symptoms, pulse, metabolism, and weight have been found repeatedly remarkably sensitive to iodine in these postoperative days, and can be increased or decreased at will, by giving or withholding the drug Our practice is to give enough to control the symptoms regardless of the metabolic rate This should be continued until the symptoms fail to return upon the omission of the drug, with us this is generally a matter of not more than a few months Sometimes the subjective symptoms can be helped by a dose of iodine so small that there is no effect upon metabolism or weight Patients often can control the dose themselves Only today I saw a postoperative patient who did not want to take three drops because, although it stopped her symptoms, it made her gain weight, which she did not want to do It is quite possible that one drop will accomplish the former and avoid the latter effect

In a few of our cases, and in relatively more in goitrous districts, the postoperative residual symptoms do not yield to iodine and gradually increase These patients in time usually show a regrowth of thyroid tissue and require further operation It is the existence of this type, particularly in goitrous regions, that gives the operation of "total thyroidectomy" some justification, in theory at least

a treatment per se, requires elucidation There are undoubtedly patients, the course of whose exophthalmic goiter is destined to be so mild that they might go through the course of their disease without inconvenience or ill effect with iodine alone for treatment If we could recognize these we might so treat them, but we cannot The fact that exophthalmic goiter starts with a mild course is no guarantee that it will so continue, and in practically every instance where, because of the apparent mildness of the disease, we have carried on with iodine alone, we have later regretted having done so

There is, however, one small group of patients that may be legitimately treated by iodine alone<sup>1, 12</sup> These are the very chronic, mild and stationary types We know that early in its course exophthalmic goiter tends naturally to remissions and relapses, and that later, even without treatment, it tends to burn itself out There are, however, a few cases in which the fire smolders on for years, true chronic exophthalmic goiter without signs of either getting worse or clearing up We have seen a few such cases where iodine relieved all symptoms, and in which they could be held in abeyance as long as the patient continued to take the drug In such cases, which are few and far between, and in no others, do I think that it is permissible to use iodine as a sole treatment for the dis-

- <sup>4</sup>STURGIS, C C, ZUBIRAN, S, WELLS, G W and BADGER, T Effects of Iodine by Mouth on the Reaction to Intravenous Injections of Thyroxin, *J Clin Invest*, 2 289, 1926
- <sup>5</sup>COLLER, F A and PORTER, E B Reaction to Iodine of Goiters from a Goiter Area, *Am J Surg*, ns 6 609, 1929
- <sup>6</sup>MAYO, C H and PLUMMER, H S The Thyroid Gland, C V Mosby, St Louis, 1926
- <sup>7</sup>THOMPSON, W O, BRAILEY, A G and THOMPSON, P K Effective Range of Iodine Dosage in Exophthalmic Goiter, *J Am Med Ass*, 91 1719, 1928
- <sup>8</sup>LERMAN, J and MEANS, J H Work in progress
- <sup>9</sup>THOMPSON, W O and THOMPSON, P K Low Basal Metabolism following Thyrotoxicosis, *J Clin Invest*, 5 441, 471, 1928
- <sup>10</sup>THOMPSON, W O and THOMPSON, P K Temporary and Permanent Myxedema following Treated and Untreated Thyrotoxicosis, *J Clin Invest*, 6 347, 1928
- <sup>11</sup>GILMAN, P K and KAY, W E Certain Advantages of Total Thyroidectomy in Selected Cases of Thyrotoxicosis of the Exophthalmic Type, *Am J Med Sci*, 175 350, 1928
- <sup>12</sup>MEANS, J H and RICHARDSON, E P Diagnosis and Treatment of Diseases of the Thyroid Gland, Oxford University Press, New York, 1929



# The Association of Chronic Ulcerative Colitis and Multiple Polyps\*

By J. ARNOLD BARGEN, M.D., and MANDRED W. COMFORT, M.D.,  
*Division of Medicine, The Mayo Clinic, Rochester, Minnesota*

IT has been shown that in 10 per cent of cases of chronic ulcerative colitis multiple polyps of the large intestine develop eventually. This estimate is based on a statistical study of 693 cases of chronic ulcerative colitis reported before this association a year ago. The patients in this series had had symptoms of the colitis for months or years and many had not had specific treatment. Just how this percentage will be altered in the future can not be foreseen, but statistics indicate that it will be reduced favorably. It is difficult also to determine what share of total so-called multiple polyposis of the large intestine or "polyposis intestinalis" this represents. An effort to evaluate this and to study factors in the origin of multiple polyps of the large intestine prompted this investigation.

Literature on the subject of polyposis of the large intestine is confusing. Classifications, such as that of Erdmann and Morris, into the adult type (acquired) and the adolescent type (congenital and disseminated), while

serving to distinguish the two generally recognized groups, seems to fall short in certain significant features. This classification fills the conventional desire of placing all polyps in main groups, but it fails to take cognizance of origin, manner of growth, or ultimate outcome of any given polyp. This, it seems, should be the aim in classifying a disease as grave as the one in question. The polyps are all of one type resulting from hyperplasia or hypertrophy of regions of intestinal mucous membrane. If classified from the standpoint of origin, they may be divided into three types: (1) those traceable to definite preexisting inflammatory disease, such as chronic ulcerative colitis, (2) those arising apparently as innumerable polypoid projections without previous demonstrable inflammation or other disease, this group should include the adolescent and familial types, and (3) those including a few disseminated, adenomatous polyps discovered either at necropsy, or in the investigation of an occasional slight hemorrhage from the rectum or a malignant neoplasm. The first type only will be considered here. Further investigation may place im-

\*Read before the American College of Physicians, Atlantic City, N. J., September 11, 1935.

inflammation as the outstanding etiologic factor in the origin of all types of polyps

Murphy stated "The etiology of intestinal polyps, like that of the common wart, is shrouded in mystery. Whence they come and why they go is like the riddle of the sphinx." Many factors, however, point to the significance of inflammatory disease or irritation of the mucosa playing a part in the etiology. The hypothesis that there is inherent weakness in cellular growth, and physiologic or chemical extraneous effects,<sup>4</sup> seems plausible but has no practical application. It is Graham's belief that irritation or infection is the basis of the growths and that those of adolescence are due to unusually sensitive mucous membranes. After a careful study of the subject, Schmieden and Westhues concluded that inflammation is the chief, but not the whole, cause. They did not agree with many authors that the Cohnheim theory of embryonal rests applies here but rather that the problem is wholly one of growth, or "misgrowth." Dukes stressed the significance of irritation, and called attention to the close similarity between intestinal polyps and the disseminated regions of hyperplasia on the skin of mice in so-called tar cancers. Erdmann and Morris also stressed the probability that all adult types of polyps could be traced to some type of irritation.

If irritation and infection are factors in the original inception of intestinal polyps, and since in 10 per cent of the cases of chronic ulcerative colitis polyps occur eventually, it would

seem that valuable information might be gleaned from a study of these cases.

Justi described "colitis hyperplastica polyposa dysenterica" in which he noted in the lining of the large intestine "plateau-like excrescences and elongated finger-like things," suggestive of polyps. He believed the condition to be the result of bacillary dysentery. His descriptions of two fatal, fulminating cases of chronic ulcerative colitis are excellent. Levin reported three cases of extensive polyposis of the colon in association with chronic ulcerative colitis and emphasized the common occurrence of these two conditions in the same patient. Cripps described a form of polyposis in which the mucous membrane has the appearance "of having been slashed into ribbons left attached at one end." He did not, nor did many of the older writers, distinguish this from the other forms of polyposis. Warwick, in considering etiology, called attention to the fact that the older observers suggested that polyps might be the result of areas of hypertrophied mucosa caught in newly formed cicatricial tissue in healing ulcers.

Saint expressed the opinion that the polyps associated with chronic ulcerative colitis are not true tumors but strips of almost detached mucous membrane and much inflammatory tissue.

Struthers, however, tried to show that chronic ulcerative colitis was one of the chief causative agents in the origin of polyps. He followed the sequence of events thus: There is first severe colitis with undermining ulcers, such ulcers may coalesce and increase in size but portions of mucosa pre-

serve their blood supply. These stud the surface of the large intestine, they heal and become round, fibroblasts are proliferated and begin to contract with resultant cicatrization, then tubules of polypoid projections are occluded, and finally Virchow's "colitis polyposis cystica" results. Elevation of these thickened and altered areas of hypertrophied mucosa results in increased friction and traction which in turn stretches the surrounding adjacent mucosa and causes the formation of pedicles.

Our observation in many of these cases convinces us that this description

of the formation of "inflammatory" polyps is adequate. Grossly (figs 1 and 2) these resemble closely the adenomatous polyps of the second group, but the dark discoloration so frequently seen in the serrated portion is absent. Microscopically the polyps are in all stages of chronic inflammation, and in the serrated portion are numerous nests or groups of glands seemingly caught in a dense inflammatory meshwork. The difference between these and the ordinary adenomatous polyps is the great increase in inflammatory and fibrous tissue in the polyps, yet multiple carcinomas have been



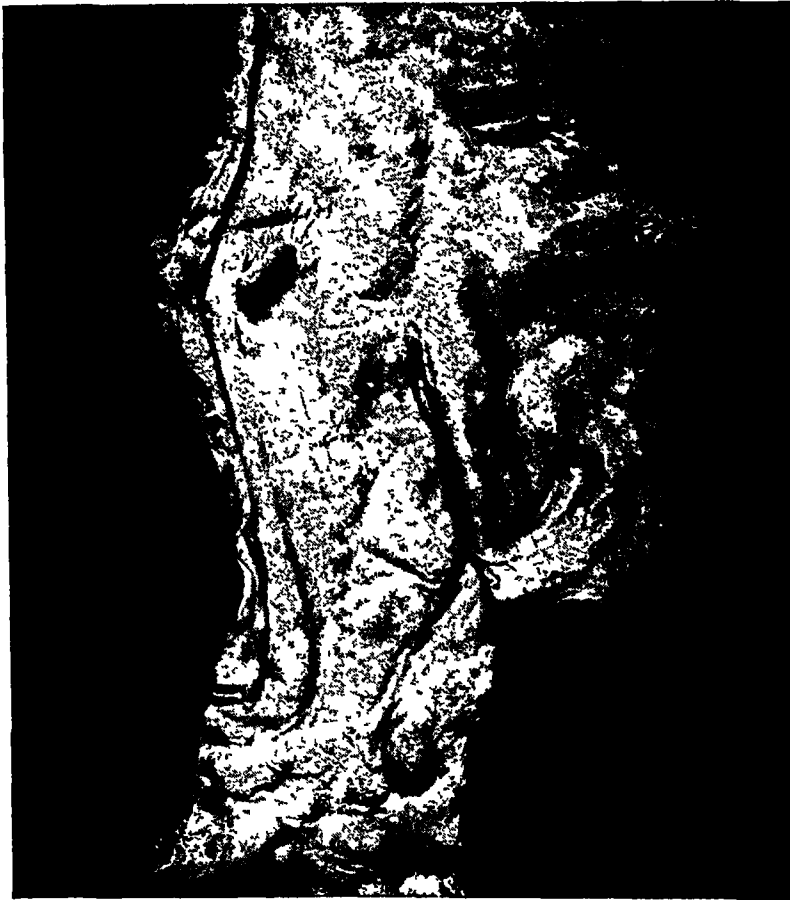


FIG 2 Portion of a colon in which the chronic ulcerative colitis has healed, leaving disseminated polyps

demonstrated in these hyperplastic areas of hypertrophy. This raises the question of whether or not these polyps are prone to malignant change.

The ratio of these to the other polyps of multiple polyposis is as 4:1, that is, of every five cases of multiple polyps observed at The Mayo Clinic, four will be on a basis of chronic ulcerative colitis. With this large disproportion of the two types, it seems important to determine whether the treatment for both should be the same. The answer to this will depend on many factors, among them, the general condition of the patient, the extent of disease, the amount of destruction of the large intestine by colitis, the activ-

ity of the colitis, and the length of time the patient has had the trouble.

The symptoms of polyposis, the result of chronic ulcerative colitis, vary little from those of actual colitis. A remission of the disease may have started and the patient gradually notices a return of bleeding, more tenesmus, frequency, and sometimes blood out of proportion to the seeming severity of other symptoms. Further proctoscopic examination reveals numerous polyps in the rectum and sigmoid of all sizes and shapes. Almost invariably they occur as healing or improvement takes place. In several instances cases of early fulminating chronic ulcerative colitis have been ob-

served from the onset, through a remission, and to the stage of polypoid change. The following case histories are illustrative.

**Case 1.** A man, aged twenty years, was admitted to The Mayo Clinic September 26, 1925. He had had attacks of bloody dysentery, with a maximum of thirty to forty stools in twenty-four hours, for nineteen months, sometimes the attacks lasted for a hundred days in succession. A diagnosis of amebic dysentery had been made although amoebae had not been found. He was acutely ill, with a maximal temperature of 102°F. The stools were mixed with pus and blood. Incontinence was troublesome. He had lost 24 pounds.

The pulse was 90, the blood pressure was 120 systolic and 90 diastolic, measured in millimeters of mercury. The abdomen was moderately tender. Proctoscopic examination disclosed diffuse, granular involvement of the mucosa of the rectum and sigmoid, edema, a tendency to hemorrhage, and scattered punched-out ulcers. A diagnosis of chronic ulcerative colitis was made. During the next five months the patient's condition fluctuated. Improvement was slow but by October 24, 1925, he was well enough to be dismissed from observation.

The patient returned in February, 1926, more seriously ill than before. He had failed steadily during the month. Proctoscopic examination showed large, sloughing, ragged, undermining ulcers of the rectum with bridging of the mucosa between large

bowel movements in twenty-four hours, the stools occasionally contained a little blood and mucus. Proctoscopic examination showed the mucosa to be practically normal, a few pitted scars were scattered over a slightly pale mucosa. There were multiple polyps from 0.3 to 0.7 mm wide and from 0.3 to 1.5 cm long, some of these bled easily. Polyposis had followed the healing of advanced chronic ulcerative colitis. Clinically the patient was in excellent condition. He was dismissed with instructions to take vaccine subcutaneously. In May, 1927, he reported that he had had the best winter since the beginning of his illness. He had gained 50 pounds and looked the picture of health. He had averaged three bowel movements daily for months and had not seen blood in his stools for at least a month. Proctoscopic examination now showed that the chronic ulceration of the colon was healed, leaving polypoid areas and polyps. Certain small polyps that were seen in January had disappeared. The mucosa between the polyps was normal except for the scars of the infection. A series of treatments by fulguration of the rectal polyps was carried out without incident. The patient was free from symptoms of bowel trouble but because all of the polyps could not be fulgurated at the first visit, he returned in December, 1927, at which time the proctoscopic examination disclosed several polyps still in the rectum but the mucosa was normal. The polyps were again fulgurated. In August, 1928, there were some scars in the rectum but no ulceration, the lumen was practically normal in diameter, and the areas fulgurated were free from polyps.

well, his weight was about normal. Gastric acids were 60 and 40, total and free, respectively, with 130 c.c. of gastric contents after a test meal. The Wassermann reaction of the blood was negative. Urinalysis was essentially negative on two occasions. The hemoglobin was 80 per cent, erythrocytes numbered 4,640,000, and leucocytes, 7,000. Three examinations of the stool on three successive days failed to show parasites or ova. There was a very small tonsillar tag which did not appear to be significant. A roentgenogram of the stomach was negative, one of the colon showed the deformity of chronic ulcerative colitis of the descending colon and sigmoid. The proctoscopic examination gave the typical picture of chronic ulcerative colitis, graded 2, with contraction to about a third the usual dimension of the rectum. Treatment consisted of the subcutaneous injection of a filtrate of the diplostreptococcus of chronic ulcerative colitis, and some kaolin and bismuth by mouth from time to time. Local rectal instillations of witch-hazel were also given. The patient was dismissed, April 29, improved. He returned, August 22, with the ulceration definitely improved, but definite evidence of disease and numerous small polyps in the rectum and sigmoid were present. Injections of the vaccine and filtrate were more or less continuous thereafter, with only the usual remissions which are allowed between. April 1, 1929, the urinalysis and blood count were within normal limits. A roentgenogram of the teeth was negative. A roentgenogram of the colon showed the deformity of chronic ulcerative colitis distal to the splenic flexure, with defects resembling polyps in the sigmoidal portion of the colon (figs 3 and 4). On proctoscopic examination the activity of the disease was graded 1. Numerous rectal and sigmoidal polyps, which were slightly larger than at the former examination, were present. April 5, the polyps in the rectum and sigmoid within reach of the proctoscope were fulgurated. Further local treatment was instituted, including the instillation into the rectum of witch-hazel, alternating with mercurochrome. The patient was dismissed May 8, improved.

Late in June, a roentgenogram taken elsewhere was referred to the clinic. The plates showed defects similar to those in the roentgenogram made in April, which suggested that there were polyps in the sigmoid beyond the reach of the proctoscope.

*Case 3.* A man, aged forty-four years, came to the clinic June 27, 1925, with a three-months' history of diarrhea. The trouble started with a slight increase in bowel movements, followed by marked constipation with severe abdominal cramps for a few days. After a laxative had been given, *rectal discharges containing blood and pus* were frequent, they were accompanied by severe abdominal pain. Three weeks before admission there had been an average of between ten and fifteen bloody, purulent rectal discharges in twenty-four hours. He had lost 30 pounds during the month before admission.

When the patient was admitted he was having an average of fifteen to twenty rectal emissions with much cramping and tenesmus. His facial expression was anxious. Proctoscopic examination revealed chronic ulcerative colitis, graded 3. The disease appeared to be in the acute stage, the rectum had a meaty appearance, and the bowel was contracted to about half the usual dimension. A roentgenogram of the thorax was negative. The hemoglobin was 50 per cent, erythrocytes numbered 3,080,000 and leucocytes 8,200. The Wassermann reaction of the blood was negative. Repeated examinations of the stool failed to reveal parasites or ova. The patient was too sick for examination by barium enema and this was not undertaken until July 28, it resulted in a diagnosis of chronic ulcerative colitis of the entire colon. A culture of the ulcers in the rectum yielded the diplostreptococcus which usually is found in these cases. Treatment was begun with vaccine filtrate. Improvement was slow but progressive. August 25, the proctoscopic examination disclosed 90 per cent improvement of the rectum. The patient was dismissed and advised to continue with vaccine treatment at home. He was examined May 11, 1926. He had improved steadily during the year and the proctoscopic examination at this time showed the activity of the disease to be of grade

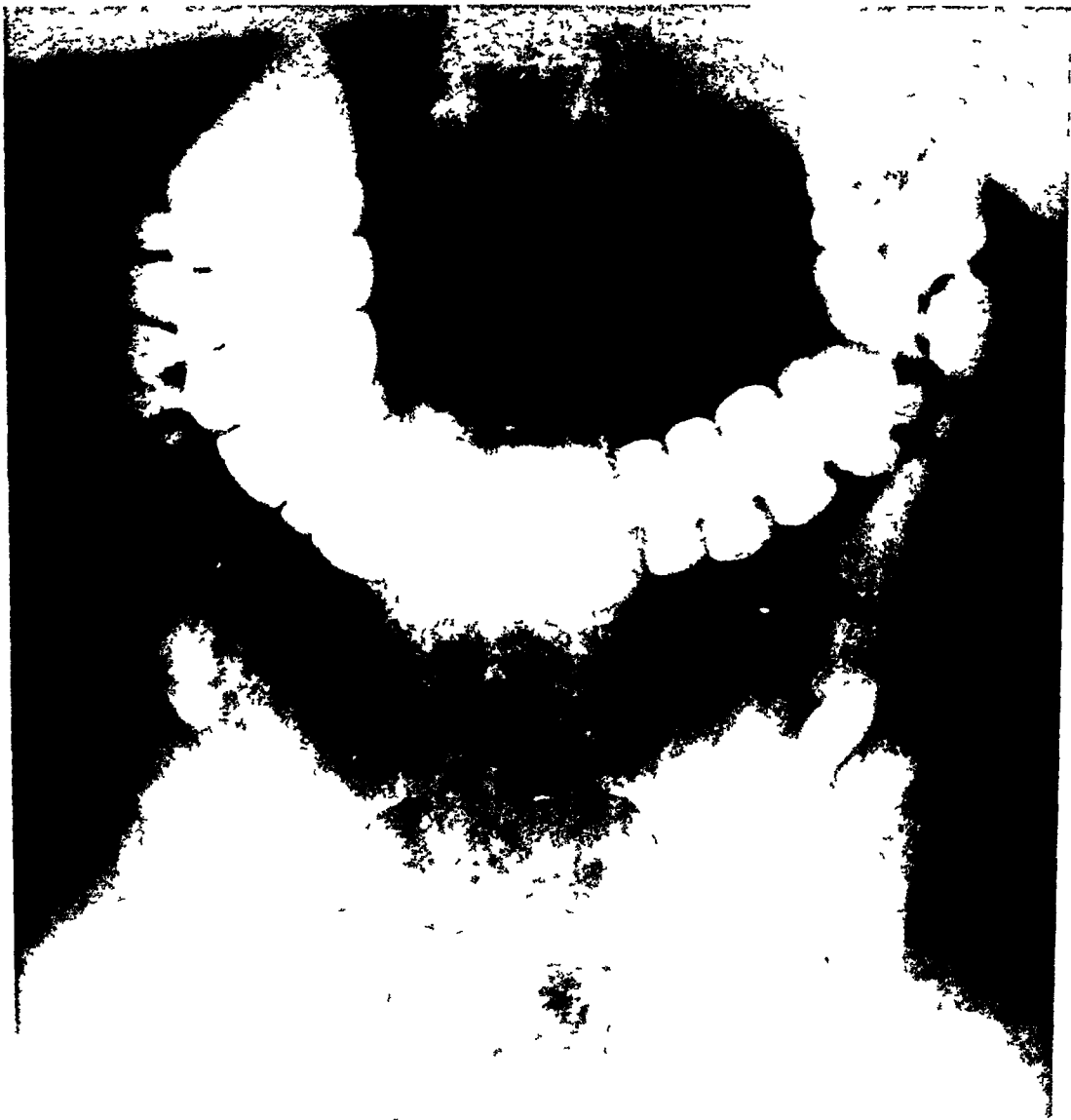




FIG 4 (case 2) Roentgenogram of colon by barium enema Defects in the sigmoid corresponding to polypoid lesions in the presence of the deformity of chronic ulcerative colitis

condition He had had the specific vaccine at intervals during this time

As in other large intestinal lesions, the roentgenogram and the proctoscope are the most valuable means of studying these polyps in the living subject Biopsy often lends valuable aid in diagnosis The proctoscope gives little evidence of the extent of the polyposis Here the roentgen ray offers the

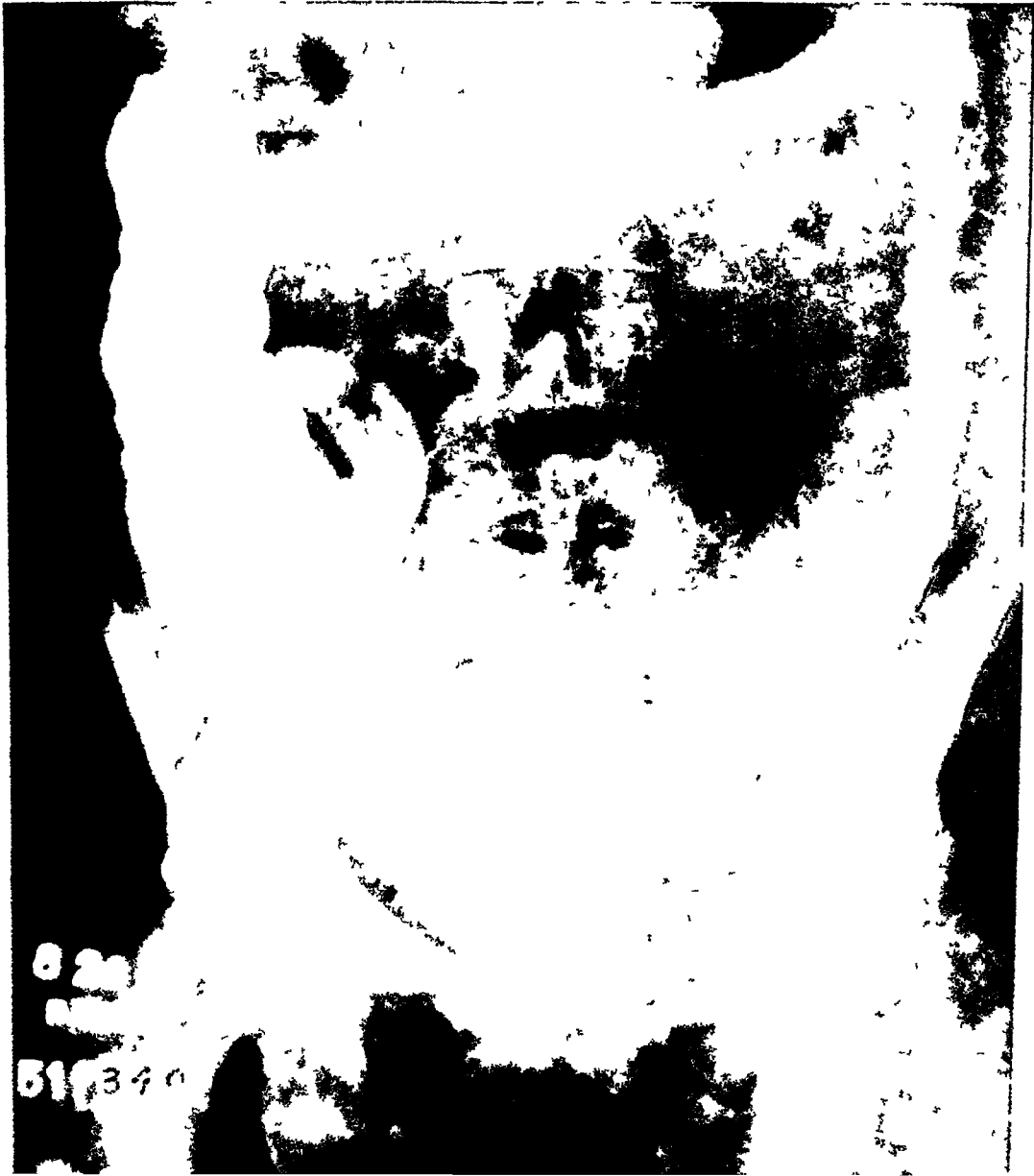
best hope of accurate information Although proctoscopic examination has greatly advanced knowledge of benign lesions of the colon, repeated instances may be noted in which, in spite of most careful efforts and by the use of all known methods, it has not been possible to obtain information of much value in some cases of polyposis of the colon In view of this, Fischer in-



jected a thin medium by rectum and then filled the colon with air. He stated that one may thus see the polyps as a spotted condition on a diffuse base. Eickenbusch was able to confirm this observation. Such slight filling with the ordinary contrast medium, he stated, gave a good picture.

Our experience, however, suggests that the best method at present is the use of the barium enema. Occasion-

ally in the cases of severe ulcerative colitis with the deep ulcers, numerous small filling defects may be seen along the margin of the intestine, not unlike the defects of polyposis, but careful observation will show distinguishing features. The edge of the colon in the case of polyposis is usually smooth, and the rounded defects are disseminated throughout the extent of the colon (case 3, figs 5, 6 and 7).



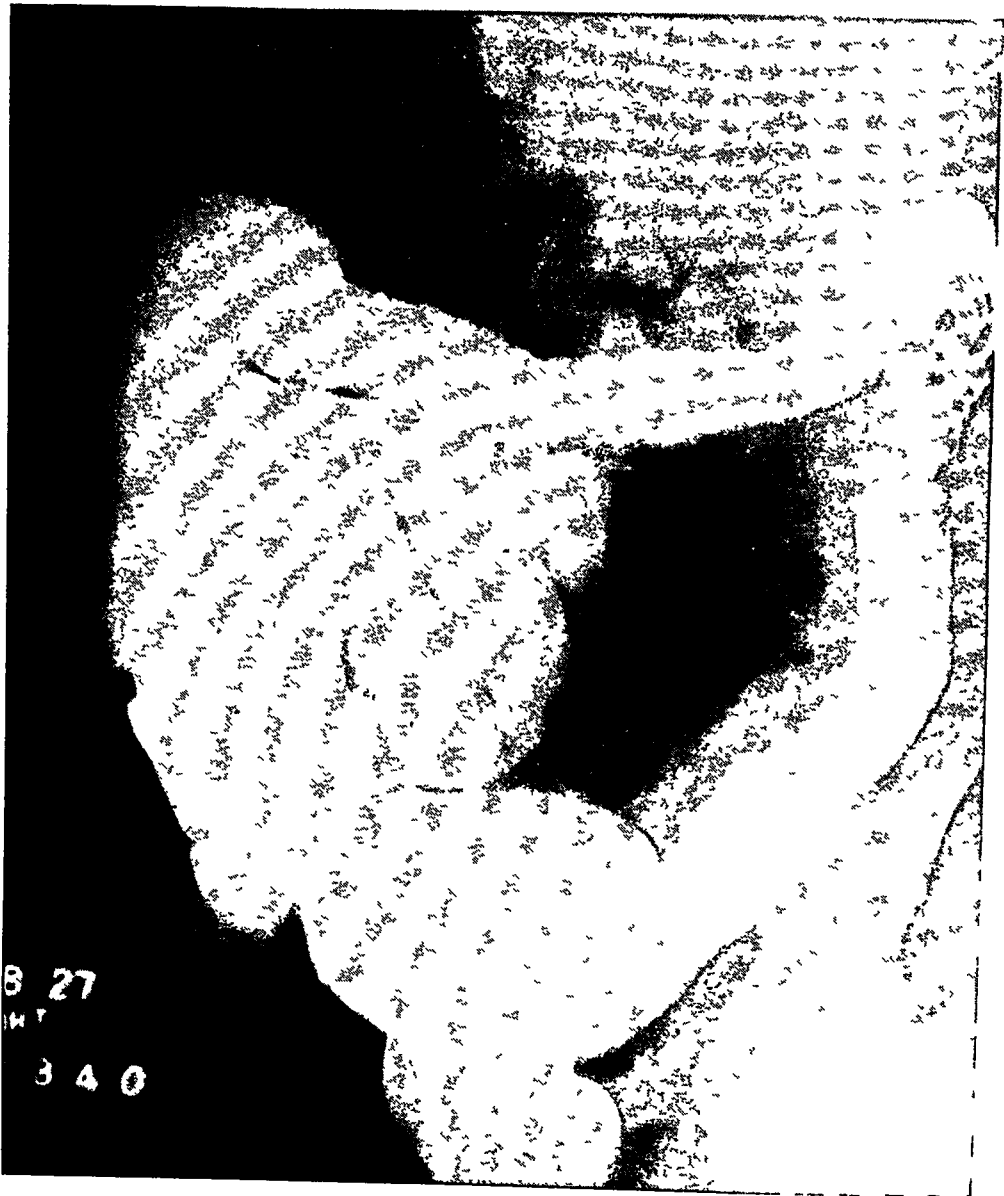


FIG 6 (case 3) Roentgenogram of colon by barium enema Beginning smoothing out of edge of colon with numerous rounded defects, in February, 1927

Polyposis in the presence of chronic ulcerative colitis may offer a grave prognosis. We are engaged at present in a microscopic study, tracing the sequence of events through the ulcerative phase to the formation of polyps, and attempting to determine the nature of these polyps. A few of the patients, like those in the cases reported, are pursuing their usual activities, and are feeling well, and yet we

know that the lining of their intestines contains polyps. We have fulgurated, as a routine, all the rectal polyps in these cases. The risk of surgical manipulation of the wall of the colon once impregnated with the residue of chronic ulcerative colitis is high. It is hoped that future work will make possible a definite prognosis in this type of polyposis.



FIG. 7 (case 3) Roentgenogram of colon by barium enema. Return of haustra but presence of numerous rounded defects, in October, 1928

#### COMMENT

Polypoid of the large intestine is present in 10 per cent of cases of chronic ulcerative colitis. It occurs after severe colitis or in long-standing, slowly progressing colitis in which there is a tendency to recurrent severe exacerbations of the disease. The polyps contain large amounts of inflammatory tissue. Proctoscopic examination is the best means of diagnosis in

most cases. Roentgenologic examination gives valuable information in many cases. We have had an opportunity to see patients in severe exacerbations of bacterial chronic ulcerative colitis, with formation of polyps later, and finally with malignant disease. Studies are under way to trace the formation of the polyps and their subsequent course in a large series of specimens obtained at operation and at autopsy.

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# Observations on the Etiology of Gall Stones\*

By E. L. WALSH, M. S., and A. C. IVY, Ph. D., M. D.,  
(*Department of Physiology and Pharmacology, Northwestern  
University Medical School*), Chicago, Illinois

THE most accepted general cause of the origin of gall stones is bile stasis. Beyond this, views vary widely. Naunyn<sup>1</sup> believes that a second cause is an ascending infection which causes "the stone-forming catarrh of the vesical mucosa," the cholesterol and calcium of the stone coming from the inflamed mucosa. Although he admits that some cholesterol may come from the bile, he attaches no great significance to diet nor to changes in cholesterol metabolism. Aschoff and Bacmeister<sup>2</sup> classify gall stones etiologically into two general divisions, (a) the non-inflammatory or metabolic, and (b) the inflammatory, believing that the origin of the cholesterol stone is due first to excessive cholesterol in the bile, plus concentration and stasis of bile in the gall-bladder. In contradistinction to these views it has been suggested recently by Halpert on the basis of his opinion that the bile which enters the gall-bladder never leaves it, that gall stones

factor, the physiologist wants to know the cause of the stasis; and second, if cholesterol metabolism is at fault, he wants to know how this affects the bile and its relation to the other biliary constituents. Our immediate interest in the problem was attracted by two reports (4, 5, 6,) in the literature, one being that human gall stones of the mixed cholesterol variety when placed in the gall-bladder of the dog disappear in several months, the second being that cholesterol stones have not been produced experimentally in the dog.

We first desired to convince ourselves that human gall stones would dissolve when placed in the dog's gall-bladder, and then to ascertain if we could influence by diet and other procedures the rate of solution, and then to study why the gall stones are dissolved, hoping that our results might throw some light on the etiology of gall stones in man and be of value in the prophylactic treatment of this disease.

placed in the gall-bladder of dogs on a diet of yellow corn-meal, bread and bone soup. The rate of disappearance was followed by use of the method of gall-bladder visualization. When the stone became quite small the stone was removed and weighed.

It was found that the stone began to lose weight within three days and in the course of from 65 to 156 days would lose from twenty to ninety-six per cent of its weight (Table 1). If, however, a definite chronic fibrous cholecystitis followed the introduction of

TABLE 1 SHOWING SOLUTION OF HUMAN GALL STONES IN GALL-BLADDER OF THE DOG  
No Solution in Peritoneal Cavity Stock Diet  
Ten stones in gall-bladder 65 days, 4 longer than 65 days  
The capital letter indicates the human source of the stone

Stone Number	Days in Gall bladder	Original Weight	Final Weight	Loss Weight	Percent Loss	Remarks
	139	2.014	0	2.014	100.0	
	156	1.000	0.074	0.926	92.6	Followed by X-ray
	113	0.896	0.111	0.785	87.5	Followed by X-ray
3 P 10	144	1.395	0.058	1.337	96.0	Followed by X-ray
3 J	65	1.124	0.141	0.983	87.5	
2 J	65	1.551	0.883	0.668	44.5	
7 K	65	1.535	0.272	1.263	82.2	
1 Y	114	0.762	0.117	0.645	84.6	
2 Y	65	1.353	0.429	0.924	61.0	
3 Y	65	2.348	2.276	0.072	3.0	Chronic*Cholecystitis
1 B	65	3.148	2.366	0.782	24.8	
	65	1.710	1.051	0.659	38.5	
1 G	65	1.286	0.359	0.925	72.0	
12 G	65	1.118	0.586	0.532	43.7	
1 S	65	3.346	3.193	0.153	4.4	Chronic*Cholecystitis
In Peritoneal Cavity						
12 G	65	1.320	1.313	loss 0.007	-0.5	
5 X	65	1.642	1.656	gain 0.014	-0.8	

\*Bile thin, low sp. gr. Note that stone did not dissolve much.

The average amount dissolved in the eight stones in normal gall-bladder for 65 days is 56.7 per cent, the maximum being 87.0 per cent, the minimum 24.8 per cent.

Stock diet consists of yellow corn meal, bread, and bone soup.

the stone, the stone lost only a small percentage (3-5%) of its weight, in which condition light yellow bile of low sp gr was found in the gall-bladder. This observation confirmed the findings of Harley and Barratt.<sup>4</sup> When gall stones were placed in the peritoneal cavity a material change in weight did not occur.

For purposes of study it was necessary to fix a uniform period of time to leave the stone in the gall-bladder. This was fixed for a 65 day period. The next factor that had to be considered was that different stones might dissolve at a different rate. On putting stones from the same patient into the gall-bladder of different dogs, or even on putting the same stone in the gall-bladder of different dogs, it was found that the rate of solution varied definitely in the different dogs, which rendered it valueless to study or control this factor.

In eight dogs on the stock diet, the average amount of the stone dissolved in 65 days was 56 per cent, the maximum being 87 per cent and the minimum 24 per cent.

*Effect of olive oil added to stock diet.* In a series of dogs 60 cc of olive oil was given the dogs, two hours before the usual stock-diet meal, to ascertain if the olive oil might have an effect on the rate of solution. The average amount dissolved in 10 dogs of this regime was 53 per cent, the maximum being 86 per cent and the minimum 21 per cent. The figures do not show that the olive oil had any influence. (Table 21.)

*Effect of cocoanut oil added to stock diet.* Because it is stated that the

people in Siam and Java only rarely have gall stones and their chief source of fat is cocoanut oil, it was decided to use this fat. Eighty cc. of cocoanut oil was given daily two hours before the stock-diet meal. The average amount of stone dissolved in 10 dogs in this series was 60 per cent, the maximum being 100 per cent and the minimum 35 per cent. Although this is 4 per cent more than the control group, we believe that it is not significant. (Table 3.)

*Does the gall-bladder of the dog secrete something which dissolves the stone?* This obviously is not an easy question to answer. In order to obtain some evidence on this question, we tied the cystic duct of five dogs, emptied the bile from the gall-bladder and introduced the stone. From 65 to 70 days later the stone was removed. Two of the five had gained from 4 to 5 per cent in weight, one was unchanged, and two lost 5 per cent. All of these gall-bladders showed pathological changes. Because of the nature of these results the question remains unanswered. Further, experiments of a direct nature are under way. However, data given later in this paper indirectly indicates that the gall-bladder does not secrete a solvent, and that the solution of the stone is caused by the bile.

*Effect of ligation of cystic duct on the dog's gall-bladder.* Because of the pathological changes that resulted following ligation of the cystic duct with a stone in the gall-bladder, we decided to ascertain the effect of ligation of the duct alone. The cystic duct was tied in four dogs, and the gall-bladder ex-

TABLE 2 SHOWING SOLUTION OF HUMAN STONES IN THE GALL-BLADDER OF THE DOG  
OLIVE OIL IN DIET  
60 cc of olive oil per day 2 hours before meal by stomach tube

Stone Number	Days in Gall bladder	Original Weight	Final Weight	Loss Weight	Percent Loss	Remarks
10	65	1 292	0 178	1 114	86 8	
3	65	2 569	0 911	1 658	64 5	
4	65	3 085	1 865	1 220	39 6	
2	67	2 943	2 319	0 624	21 1	Adhesions-Moderate Cholecystitis
4 X	65	2 039	0 365	1 674	82 3	Pregnant
10 G	65	1 119	0 727	0 392	35 0	Slight Cholecystitis
7	65	1 806	1 187	0 619	34 2	Slight Cholecystitis
2 CC	66	1 176	0 557	0 619	52 5	
13	65	2 853	1 463	1 390	48 7	Slight Cholecystitis
1	65	3 643	3 319	0 324	8 8	Marked Cholecystitis-Adhesions
1 Y	65	2 130	0 605	1 525	71 6	

The average in 10 dogs, omitting Stone 1 because of the marked cholecystitis, is 53 6 per cent, maximum 86,8, minimum 21 1

Compare with Table 1, noting that cholecystitis is apparently more frequent in this series

amined two months later In one the gall-bladder had been replaced by fibrous tissue. In the others the gall-bladder wall was thickened and the mucosa abnormal The gall-bladder in each case contained a colorless or light brown viscid secretion and small flecks or concretions of pigment and carbonates, the largest concretion weighing 0 184 g

*Effect of stricture of common bile duct on rate of solution of human gall stone:* A stricture of the common bile duct was produced in four dogs by inserting a glass cannula having an in-

side bore of 1 mm into the common duct This produced a stasis of bile which was demonstrated by the fact that the bile ducts above the point were dilated and from 50 to 100 mgm of "flaky" sediment of the pigment and carbonate variety was found in the gall-bladder when the dogs were autopsied from 61 to 70 days later. The average loss of weight of the stones was 44 per cent which is less than that of the control dogs without stricture on the same stock diet This is not as marked an effect as we had anticipated. Our explanation will be offered later Further experiments on this



TABLE 3 SHOWING SOLUTION OF HUMAN STONES IN THE GALL-BLADDER OF THE DOG  
COCOANUT OIL IN DIET

80 cc of cocoanut oil per day 2 hours before meal by stomach tube.

Stone Number	Days in Gall-bladder	Original Weight	Final Weight	Loss Weight	Percent Loss	Remarks
3 Y†	65	1 072	0 245	0 727	67 6	Followed by X-ray
100*	65	2 488	1 604	0 884	35 4	Marked Cholecystitis
7	65	1 167	0 211	0 976	82 3	
OSM	65	4 709	3 948	0 761	16 3	Moderate Cholecystitis Stone adherent to GB in several small areas
12	66	2 827	1 077	1 750	62 0	
1 GO	67	1 543	0 945	0 598	38 4	Moderate Cholecystitis
3 X	65	2 019	0 887	1 132	56 0	
4 CC	68	1 147	0 596	0 551	49 1	
10 CC	65	1 194	None	1 194	100	Lymphoid-Hyperplasia marked
1 BG	67	1 457	0 825	0 632	43 3	
13 CC	50	0 982	0 319	0 663	71 5	

†This dog is the same as 1 B in Table 1. Note Dissolved 67 per cent the first time and 24 the second time

\*This dog is the same as 1 G in Table 1. Note Dissolved 72 per cent the first time, 35 per cent the second time with cholecystitis

The average for this group, omitting dog OSM and dog 13 CC, nine dogs, is 50 3 per cent, maximum 100 per cent, minimum 35. Including dog 13 CC, average is 60 5 per cent

question are in progress in which the procedure is modified. (Table 4.)

*Effect of stricture of common bile duct on gall-bladder of the dog* A stricture of the common bile duct was produced in seven dogs by the method used above (Table 5). Two of the animals died in 49 and 62 days respectively, one of empyema of the gall-bladder and multiple liver abscesses and the other of bile peritonitis due to a small opening (0 5 mm diameter) in the common duct. The other were killed from 62 to 80 days after the op-

eration. The ducts of all the dogs were dilated and sediment in amounts varying from 50 to 100 mgm was found in the gall-bladder as well as in the dilated common duct above the cannula. A hyperplasia of the lymphoid tissue and of the mucosa of the gall-bladder was found in three of the five dogs. In the other two the mucosa was normal. The result alone, with those just mentioned above, how the stricture produced by the method may cause changes in the histology of the gall bladder mucosa and

**TABLE 4 EFFECT OF STRICTURE OF COMMON BILE DUCT ON SOLUTION OF HUMAN STONE IN DOG'S GALL-BLADDER  
Stock Diet**

Dog Number	Stone Number	Days in Gall bladder	Original Weight	Final Weight	Loss Weight	Percent Loss	Remarks
143	5 CC	69	1 178	0 813	0 365	44 9	Pericholecystitis
167	A P	64	0 830	0 224	0 606	74 2	Gall-bladder normal
173*	P R	61	2 019	1 486	0 533	26 4	Bile very thick
140	1 M	70	1 147	1 000	0 497	33 1	Gall-bladder normal Lymphoid Hyperplasia

\*Round worm in gall-bladder 2 inches long In all these dogs there was 50 - 100 mgm of flaky sediment of the nature of calcium-pigment and X-CO<sub>3</sub>, which is abnormal for the dog's normal gall-bladder Average 44%

**TABLE 5 EFFECT OF STRICTURE OF COMMON BILE DUCT ON GALL-BLADDER OF THE DOG**

Dog Number	Time of Observation Days	Findings
118	62	Bile peritonitis Slight cholecystitis Dilation of ducts. Sediment in gall-bladder
188	80	Killed Gall-bladder normal Ducts dilated Sediment in gall bladder
134	64	Killed Gall-bladder thin wall Normal mucosa Bile very thick with mucin Ducts dilated Sediment in GB Suspended in bile
144	67	Killed Lymphoid hyperplasia Sediment in gall-bladder Ducts dilated
145	68	Killed Lymphoid hyperplasia Bile very thick and flaky with sediment Ducts dilated
163	49	Multiple liver abscesses Empyema of the gall-bladder
165	67	Killed Hyperplasia of mucosa Ducts dilated Sediment in gall-bladder

Sediment was found in every gall-bladder either in the mucous along the mucosa or suspended in the bile The sediment varied from 50 to 100 mgm in amount and was of the calcium-pigment and X-CO<sub>3</sub> variety

lymphoid tissue and in the character of the bile.

*Effect of chronic reverse duodenal peristalsis on gall-bladder:* The above method of producing stasis was anatomical and rarely occurs in life. Since duodenal motility is concerned in controlling the flow of bile from the biliary passages, it was thought that by permanently altering duodenal motility we might cause a biliary stasis. In order to permanently alter duodenal motility a two inch loop of duodenum was excised and turned end-for-end and sutured, or a reversed duodenal loop was made. In the duodenum then there existed a continuous reverse peristalsis leading to duodenal stasis and abnormal motility. In the course of eight months this leads to a marked hyperplasia of the gall-bladder mucosa and lymphoid tissue, (Dr. L. A. Crandall and E. L. Walsh) and on autopsy the bile is found to be thick and contains sediment of the pigment and carbonate type.

In this type of experiment, in which the disturbance is more of the nature of perverted physiology, one obtains the same results as in the mechanical or anatomical stricture, and reverse peristalsis in the duodenum is known to occur in nausea, vomiting and in the morning sickness of pregnancy.<sup>7, 8</sup>

*Experimental chemical acute cholecystitis and rate of solution of gall stones:* Acute chemical cholecystitis was produced in three dogs each with alcohol and Dakin's solution. The results showed that the cholecystitis had to be diffuse and considerable connective tissue proliferation present before the rate of solution of the stone was

affected. Three dogs, in which there was marked hyperplasia of the mucosa, hyperplasia of the lymphoid tissue and slight fibrosis, dissolved from 59 to 100 per cent of the stone in from 55 to 70 days.

It was evident from these experiments and the observations recorded above that if the gall-bladder could concentrate bile the stone would be dissolved rapidly, but if it could not concentrate the bile very little of the stone would be dissolved.

#### IN VITRO EXPERIMENTS

The observations above indicate that there is something in dog's gall-bladder or concentrated bile which is responsible for dissolving the stone.

It has been found that ox bile,<sup>10</sup> dog's bile,<sup>10</sup> soap solution,<sup>9</sup> have a solvent action on human gall stones. It is claimed that sodium taurocholate and glycocholate have a slight solvent action and that sodium desoxycholate has 3 or 4 times the action of the other bile salts.<sup>11</sup>

The results of our in vitro experiments are shown in Table 6.

It is to be noted, (1) that we failed to find the two chief bile salts (Merck) present in bile to possess a solvent action; (2) that human bile caused no solution; (3) that dog's gall-bladder bile caused solution and (4) that when diluted dog's gall-bladder bile or the dog's hepatic bile was used no solution of the stone occurred. This confirms our in vivo observation that the concentration of the bile by the dog's gall-bladder is essential for solution of the human gall stone. It also shows that the lower concentration of cholesterol in dog's bile than in human bile

TABLE 6 EFFECT OF VARIOUS SOLUTIONS ON GALL STONES WHEN SHAKEN IN VITRO FOR 15 DAYS AT 37°C

Solution Used—Solution Changed Daily Solution Agitated	No of Expts	Av % Loss	Av % Gain	% Max Loss	% Max Gain	% Min Loss	% Min Gain
Distilled water	2		03		07	01	
0.9% Sodium chloride in water	4	01		02			00
1% Sodium glycocholate in water	4		01		04		00
1% Sodium taurocholate in water	4		02	03	06		
Human fistula bile	4	01		07	02		
Human gall-bladder bile	8		01	03	07		
Dog's fistula bile	8	16		43		04	
Dog's gall-bladder bile	12	28.8		82.0		11.8	
Dog's gall-bladder bile diluted 10 times with water	5		05	05	26		
1% Butyric acid in pH 6 buffer solution	4		11.1		29.8		05
1% Butyric acid in pH 8 buffer solution	4		8.3		14.0		05
1% Oleic acid in pH 6 buffer solution	18	13.6		41.1		5.8	
1% Oleic acid in pH 8 buffer solution	18	25.1		72.5		4.2	
1% Myristic acid in pH 8 buffer solution	11	27.4		41.7		12.1	
1% Lauric acid in pH 8 buffer solution	13	74.8		100.0		50.6	
Solution Changed Every 3 Days							
1% Myristic acid in pH 8 buffer solution	5	10.9		14.1		5.6	
1% Lauric acid in pH 8 buffer solution	7	29.5		39.8		20.0	
Solution Changed Every 3 Days—No agitation							
1% Lauric acid in pH 8 buffer solution	2	7.6		8.5		6.7	

is not the factor, because if it were a factor, then the stone should dissolve faster in the more dilute hepatic bile of the dog than in the more concentrated gall-bladder bile.

The various fatty acids shown in Table 6 were examined for their solvent action because we thought that the fatty acids and soap fraction of the bile which is higher in the dog than

in man, might be the important factor. To our surprise the stones gained weight in the butyric acid solution, but, however, lost weight in oleic acid, the chief fatty acid in olive oil, and in myristic and lauric acid, the chief fatty acids in coconut oil. The solvent action of lauric acid is to be especially noted. It is also interesting that the pH of the fatty acid solution is also

important in that there is more of the soap of the fatty acid present in the pH 8 buffer solution than in the pH 6 buffer solution.

Table 7 shows that stones from different patients differ in the rate at which they lose weight, but the difference is not as marked as we had anticipated.

#### CHEMICAL ANALYSIS OF BILE

Since soap from the above results has such a solvent action on human gall stones of the cholesterol-pigment-calcium variety, studies on the relative amounts of cholesterol on the one hand and the saponifiable substances on the other in human and dog's bile was undertaken

The data obtained are shown in Table 8. In the dog the ratio of saponifiable substances to cholesterol

is approximately 20 to 1, whereas in man it is only approximately 2 to 1.

Our results indicate that the soap-cholesterol ratio in bile is very important and that an optimum concentration of soap is necessary for the solution of the human gall stone. Soap is the best solvent we have yet used which is confirmatory of the observation of Brockbank.

We have attempted to determine the soap content of human and dog's bile, but have been unable to obtain a method that would yield accurate results. The older values of soap in the bile, we believe, are unreliable.

#### CONCLUSIONS AND SUMMARY

1. Human gall stones of the mixed cholesterol variety are dissolved when placed in the gall-bladder of the dog, confirming Harley and Barratt,<sup>4</sup> Labes<sup>5</sup> and Harrison and Barber.<sup>6</sup>

TABLE 7 SHOWING THAT THE RATE OF SOLUTION OF STONE DEPENDS TO SOME EXTENT ON THE STONE

Averages are taken from daily weighing of stone until completely dissolved. The latter indicates that the stones were from the same patient. In vitro experiments with lauric acid in pH 8.0 buffered solution, solution changed daily.

Stone Number	Original Weight	Days for Complete Solution	Average Loss per day in mgm
1 L	0.830	34	24
2 L	0.962	35	27
1 M	1.182	38	31
2 M	1.232	40	30
1 P	1.153	27	43
2 P	1.512	39	39
1 Q	0.924	38	24
2 Q	1.085	35	31*

\*Some fragmentation occurred which could not be checked by weight and accounts for the discrepancy.

TABLE 8 RESULTS OF CHEMICAL ANALYSIS OF HUMAN AND DOG GALL-BLADDER AND FISTULA BILE.

Saponifiable and Non-saponifiable Fractions  
Saponifiable fraction weight checked by titration  
GALL-BLADDER BILE

Case Number	Human		Dog	
	Post mortem Bile			
	Non-saponifiable Cholesterin	Saponifiable Fat, fatty acid, Soap, lecithin	Non saponifiable Cholesterin	Saponifiable Fat, fatty acid, Soap, lecithin
1	0 358	2 066	0 188 0 140	4.016 3 544
2	0 972 1 296	1 104 1 440	0 106 0 108	4 428 4 488
3		1 136 1 148	0 086	4 220 4 294
4	0 602 0 578	1 670 1 692	0 136	3 740 3 754
5	0 162 0 134	0 684 0 619	0 354 0 356	3 926 3 858
6			0 108 0 102	3 920 3 938
7			0 132 0 130	4.268 4 172
Average	0 586	1 284	0 162	4 040

FISTULA BILE

Case	Human		Dog	
		Cholecystostomy		Common Duct Gall bladder removed
1*	0 162 0 179	0 514 0 526	0 019 0 015	0.485 0 452
			0 020 0 032	0 495
			0 017 0 017	0 259 0 257
			0 032 0 030	0 094 0 160
Average	0 171	0 520	0 020	0 314

\*Probably concentrated 2 to 4 times by passage through gall-bladder

2. A diffuse fibrous cholecystitis prevents the solution of the gall stone, which is due to the failure of such a gall-bladder to concentrate the bile. Concentration of the dog's bile is necessary for solution of the gall stone

3. We were unable to show that the addition of olive oil or coconut oil to the diet significantly altered the rate of solution of the stone. However, this does not show that such vegetable oils might not be of prophylactic value, since the presence of the gall stones in the gall-bladder caused changes in its histology

4 Biliary stasis if it leads to a definite cholecystitis in the dog definitely delays the solution of the gall stone

5 Biliary stasis leads to histological changes in the gall-bladder of the dog

6. The difference in the cholesterol content of dog's bile and human bile per se does not explain why dog's gall-bladder bile dissolves the human gall stone

7 Soap, especially the soap of lauric

acid, is a potent solvent of cholesterol and the mixed type of human gall stone.

8. There is a marked difference between the cholesterol-saponifiable ratio in human bile and dog bile, which we believe explains why gall stones of the cholesterol variety have never been produced in the dog and why the dog's gall-bladder dissolves the human gall stone. We have not proved this, however.

9 The hope of preventing gall stones or of reducing their incidence in pregnancy, or even of dissolving them, is not a "pot of gold at the foot of the rainbow," since it is known that diet influences the cholesterol output in the bile, that the reason why the dog's gall-bladder dissolves the human gall stone is within the realm of the ascertainable, that biliary stasis is preventable, and that the incidence of gall stones in the United States is much higher than in certain Oriental peoples whose diet is quite different from ours

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# Later Results in the Use of Stramonium in Post-Encephalitic Syndrome\*†

By A L JACOBSON, M D , and F EPPLEN, M D , *Seattle, Washington*

IT IS now a year since we began using stramonium in the treatment of Post Encephalitic sequelae, the first report being read at the 1929 meeting of the American Medical Association in Portland. At that time ninety three per cent of our cases were of the Parkinsonian syndrome, largely because our material came chiefly from the King County Hospital, where a number of these cases had accumulated, and partly because certain cases in that hospital available to us had not been worked over carefully enough to determine that they were post encephalitic in nature, the patients being stowed away in self care wards, pensioners of the hospital. Clearing up the diagnosis on these revealed others of various types.

Price<sup>1</sup> enumerated and classified the various syndromes according to the type or the system involved as follows (1) motor, (2) sensory, (3) psychic, (4) ocular, (5) aural, (6) respiratory, (7) glandular (hypophyseal), and those of the (8) vegetative system, to which should be added a (9) miscel-

laneous group. According to Price, only 54% present the Parkinsonian syndrome, 35% some form of excito-motor phenomena, leaving 13% for the miscellaneous group.

The Parkinsonian syndrome is made up of excito-motor phenomena and often shows an admixture of ocular, paretic and phenomena attributable to the vegetative nervous system, e.g. sweating, salivation. Furthermore the Parkinsonian syndrome resembles Parkinson's Disease only in part, the tremor being coarser in the former, the onset and progress differing. Most typical of all differences is the fact that Parkinson's Disease appears late in life, the syndrome at almost any age, our youngest being fourteen. Some of the types, notably the psychic, the glandular and aural types, did not fall into our hands.

Case five of our previous paper belongs to the excito-motor phenomena group. He had a blephorospasm with oculogyric phenomena that partially incapacitated him, and has since then developed a slow, grinding tic of the lower jaw. He reports that this had been present for some six months six years ago and disappeared spontaneously. These movements are slow and occur several times an hour, the

†Presented at the Minneapolis meeting of the American College of Physicians, February 10, 1930.

<sup>1</sup>Unpublished paper read before the King County Medical Society Jan 6, 1929.



patient is conscious of them but they are beyond his control. They appeared and continue in spite of a regimen of stramonium.

Another patient who is on stramonium is developing a rigidity of the tongue, characterized by him as a fixation, which interferes with mastication and articulation; he also has a typical Parkinsonian syndrome which had very largely yielded to the treatment.

A third patient with a Parkinsonian syndrome, had a habit like tic of the tongue, which consisted of licking the lip and chin every two or three minutes. This symptom was lessened in frequency and degree by stramonium, as did her Parkinsonism.

A fourth patient has a tic of the lips associated with fatigability, both of which were lessened but not eliminated by stramonium.

Of the ocular type, we have seen two cases with oculogyric crises, one upward, the other upward and outward. Both of these cases, more especially the latter, were greatly improved on stramonium.

The respiratory type constitute an interesting group. We have seen only one, a patient on stramonium for post encephalitic fatigability, suddenly, while engaged professionally, developed very deep, slow, slightly irregular dyspnea without cyanosis. This patient had had periodic sighing respiration for about two months preceding. Neither phenomenon has recurred though the patient is no longer taking stramonium.

Vegetative nervous system disorders are usually part and parcel of the Parkinsonian syndrome, notably sweating

and salivation, both of which have yielded to stramonium.

Under the miscellaneous group we saw three, two of cerebellar syndrome with ataxia, anergia, dysmetria, incoordination and explosive speech, and one with a group of symptoms almost identical with those of myasthenia gravis: none of these yielded to stramonium.

The ideal cases for medication by stramonium are those of the Parkinsonian syndrome group. Remarkable as it may seem, the worst cases improve the most, and again the very young do exceptionally well. This was well exemplified in a boy of fourteen and a girl of nineteen, both severe cases were rendered almost normal while on large doses, sixty minims four times per day. Both retained a tendency to propulsion and slight tremor, and the boy a slight incoordination, possibly a cerebellar admixture.

Case 1 of our previous series, a patient who was bed-ridden 90% of the time, is now an inmate of the poor farm where it is a prerequisite that they are capable of complete self care. Prior to the use of stramonium he was completely dependent upon attendants (Moving pictures will be shown of this man). Case 2, likewise completely dependent upon attendants before taking stramonium, is now doing housework and succeeding in pleasing his mistress. Both these patients from a complete obliviousness to environment, now play cards and checkers (as will be shown) listen to the radio, attend moving picture theaters, and otherwise demonstrate their interest in life. Case number 6, previously reported, was an automobile mechanic,

disabled to the degree that he could do a few chores about the house, is now able to earn a part of his former salary at his trade

Our worst case, not previously reported because of space limitations by the editor, bedfast, speechless, with a tremor grotesque in degree, dysphagia limiting his foods to liquids, emaciated, soiling himself constantly because he could not tell of his needs, has been benefitted to the degree that though still bed-ridden, he can speak intelligently to his attendants, is clean, eating and gaining weight. His tremor greatly diminished and his bradykinetic movements so much improved that he can perform certain duties for himself, notably eating

A woman of 56 with marked tremor, unable to feed herself or walk, very weak and fatigable, the victim of a spinal myalgia requiring morphine, has on stramonium overcome the necessity for opiates, walks and feeds herself and is much less fatigable

We have now had forty six cases in the hospital and in private practice and have seen twenty others in consultation. Seventy per cent were Parkinsonian syndromes, and only one of which did not get some benefit, to be sure, it was often slight. This was especially true if the patient was young but remarkably great as improvements go in neurology. One patient with a strabismus and one with a hemiparesis were wholly benefitted. So far as these symptoms went these two were more euphoric and had lessened muscular rigidity and were improved in their mental responsiveness. Three cases, of the non-Parkinsonian type of miscellaneous cases were entirely un-

benefitted. This makes about 11% with no benefit. The others were all benefitted from a trifle to a great deal

#### TECHNIC

We have been using U S P standardized preparations, specifying a fresh preparation, in doses beginning in adults with twenty measured minims three to four times daily until an optimum dosage is reached, which is usually around sixty measured minims four times daily to get the best results. We have not gone beyond this though it may be necessary on occasion

In a few of our cases sufficient tolerance has developed so that the dose has had to be increased after a few months. This has been progressive in these cases. Sixty minims have been increased to seventy, then to eighty and then to ninety minims

Sometimes the relief from tremor in Parkinsonian syndromes is only slight when stramonium is used in spite of striking benefit to the rest of the symptom complex. In these cases it is well to add scopolamine to the medication. We have seen no other indication for the addition of this drug, though Garnett Cheney<sup>2</sup> uses it quite frequently. Our routine, after the optimum dose of stramonium is ascertained and tremor has not satisfactorily subsided, is to add scopolamine 1/150 grain once or twice daily increasing first to 1/120, then to 1/100, later to 1/75 and occasionally to 1/60 grain once or twice daily until the maximum inhibition of tremor is attained or until toxic manifestations preclude large doses. It is striking how after 1/100 grain scopolamine has been added to the morning dose of stramonium it will

<sup>2</sup>Jour. A M A Vol XCIII, 1929, p 2030

eliminate or almost eliminate the troublesome tremor all day. Occasionally the larger doses given twice per day are necessary. Scopolamine, however, does not relax the muscular rigidity and other symptoms nearly as well as does stramonium.

Toxic manifestations from stramonium have been noted. Nausea prevented one case of Parkinsonism from continuing. Mydriasis is always present and troublesome for a time. Contrary to expectations, this usually disappears later in spite of increasing dosage. The ciliary muscle seems to accustom itself to the intoxication remarkably well. Eserine has been recommended, we have found it necessary to counter-act the pupillary dilatation by this drug but once. We used it but once per day in our patient, the young boy previously mentioned and it held the pupils down all day. Several times we have seen cerebral excitation and flightiness with a subjective sensation of nervousness, this necessitated reduction of the dosage. Dowling, of Seattle, reported to us a case of intoxication in a patient who had been on large doses of stramonium without untoward symptoms until she had her

prescription filled in a smaller city whereupon she promptly developed symptoms of atropine poisoning. The drug was not analyzed but it is presumed that tr. of belladonna was substituted for the better suited, less toxic, but less used stramonium. Some patients have reported diarrhea but it has not been a troublesome symptom. Marked dryness of the mouth associated with a bitter taste is a constant toxic manifestation, even in patients who had been previously suffering from hyperptyalism.

#### SUMMARY

1. We still regard stramonium as a valuable drug in palliation of the Parkinsonian syndrome and associated symptoms.
2. Very large doses are necessary.
3. Toxic manifestations are rare and seemingly evanescent.
4. Fresh preparations should be demanded.
5. Particular caution is necessary against substitution of belladonna for stramonium.
6. There are probably at present unknown alkaloids present in stramonium.

# Curing the Ulcer Patient\*

By SEALE HARRIS, M D , *Birmingham, Alabama*

CURING the ulcer patient does not consist merely of giving him a routine diet copied from some text book, and prescribing stock prescriptions for alkalis, nor does a gastro-enterostomy, or even resection of the ulcer bearing tissue always result in permanent relief. It is true that many ulcer patients get well and others receive temporary benefit from rest and diet, and surgery relieves many permanently, and others temporarily, but there is still too large a proportion of ulcer patients who receive no permanent benefit from either medical or surgical treatment.

Sir Berkley Moynihan<sup>1</sup> in discussing "the necessity of understanding between the physician and surgeon" says "The problem of the treatment of duodenal ulcer is one which concerns both the physician and surgeon. A good understanding between them is essential to the welfare of the patient."

"I think it is a reproach to medicine that the surgeon should be compelled to operate so frequently for gastric and duodenal diseases. Such ulcers ought surely to be cured, far more often than they are, by medical treatment."

Eusterman<sup>2</sup> in discussing late recurrences following gastro-enterostomy expressed the opinion shared by most clinicians who see the bad results of the careless, unscientific management of ulcer patients both by physicians and surgeons when he said: "The so-called medical treatment of ulcer has been incomplete, haphazard, and largely aiming at symptomatic relief in 90% of patients;" and he adds that "the complication or sequellae after surgery may be appreciably reduced by proper medical management."

Until recently, we have not had an efficient follow-up system of our own ulcer cases, and we do not know how many recurrences we have had after medical treatment, but they have occurred too frequently. Likewise we have not tabulated the number of recurrences or failures to cure, in ulcer patients who had been treated by others before they came to our Clinic, nor have we yet examined our records for the number of surgical failures that we have been called upon to treat. We are convinced, however, that during the past year we have had more recurring, or uncured, ulcers to treat than ever before; and therefore we have done some serious thinking regarding the causes of medical and surgical failures in the management of ulcer patients.

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\*Read before the Fourteenth Annual Clinical Session of the American College of Physicians, Minneapolis, Minnesota, February 10-14, 1930

## EARLY DIAGNOSIS

One of the reasons for the failure to cure gastric and duodenal ulcers, particularly the latter, is that the diagnosis is rarely made by the general practitioner until the lesion has existed for years, when there is organic pyloric stenosis or there are chronic inflammatory changes around the crater of the ulcer that prevent healing.<sup>3</sup>

The old text book triad of ulcer symptoms, i e., pain, vomiting, and hemorrhage is still the criterion by which many physicians diagnose ulcer. In reality, vomiting and hemorrhage are late symptoms, and usually the ulcer has existed for years before the pain becomes severe enough to impress the patient with the fact that his recurring periods of discomfort, or slight pain two or three hours after eating relieved by taking food, or soda, alternating with months of euphoria, is any more serious than "just a little indigestion."

It is probable that most ulcers of the duodenum, and perhaps some gastric ulcers, if diagnosed early, may be cured by giving the patient frequent feedings of milk, or other bland food, while the patient continues his work, provided that foci of infection, which may be the cause of the ulcer, are removed, and the patient's eating and other living habits are corrected. Usually, however, by the time a patient consults a gastro-enterologist, or a surgeon, the time has passed when the ambulant treatment can accomplish anything, and the patient has to submit to a strict diet that can rarely be carried out, except in a hospital, or he must submit to surgery for relief.

Friedenwald and Finney<sup>4</sup> made a study of 1000 cases of ulcer and the average duration of symptoms of their patients was over ten years. The Mayo statistics<sup>5</sup> showed the average duration of symptoms of their ulcer patients was over nine years. Ulcer patients postpone surgery as long as possible and usually consult the physician earlier, and some years ago a study of several hundred of our cases showed the average duration of symptoms was a little more than five years.<sup>6</sup>

Alvarez<sup>7</sup> in one of the sanest articles that has been written on the treatment of duodenal ulcer says. "Out of 100 patients studied at the Mayo Clinic, in only fifty had changes been made in their diet, and forty-eight had been practically untreated. They had suffered for an average of ten years and had seen an average of four physicians. The diagnosis had been made in thirty-three cases and suspected in twenty-nine more."

"The failure to recognize the disease can be ascribed to the fact that the clinical picture of duodenal ulcer is inadequately described in text books, and the failure to treat ulcer intelligently is due to the deficiencies of text books which describe only one type of management and that one which is not practical for most patients."<sup>11</sup>

*Finding and Removing the Cause*

Perhaps the reason for some of our failures to cure peptic ulcers is because our attention has been focused too much on the ulcer itself, and we have forgotten sometimes the patient bearing the ulcer, and likewise sometimes we have lost sight of the car-

dinal principle in the treatment of all disease, i e, find the cause and remove it

It is true that rarely can we locate with certainty the actual cause of the ulcer in a given case, but if we study the eating and living habits of the patient, and teach him the personal hygiene necessary to build up his resistance to infections and remove the foci of infections that exist when treatment is begun, we have contributed much to his chances for cure whether treated medically or surgically

Medical literature is plethoric with discussions of various theories on the etiology of peptic ulcer, though very little has been proved that will account for the apparent increase in the number of cases. The work of Rosenow<sup>8</sup> which has been verified by a number of other research workers<sup>9</sup> seems to make it certain that infection is present in all cases and that the streptococcus viridans, or other pathogenic organism is the probable exciting cause of gastric and duodenal ulcers. It likewise seems certain that there is an underlying local or constitutional condition that lowers the resistance of the individual to the infections that produce ulcer.

Dantzer<sup>10</sup> believes that we should regard ulcer as a constitutional condition, with an abnormality of the circulation in the mucosa of the stomach as the predisposing cause. Many others hold to the theory of vascular changes in the ulcer bearing area as being the essential factor in the pathogenesis of ulcer, but what is the cause of the circulatory pathology, both local and constitutional?

### *Vitamin Deficient Diets*

It certainly is a fact that the eating habits of most ulcer patients need to be corrected, and some of the facts brought out in recent studies of nutrition, particularly with reference to diets deficient in vitamins seem to indicate that one of the important predisposing causes of ulcer is the general use of devitaminized foods<sup>11</sup>

About fifteen years ago, McCollum, Simons and Parsons<sup>12</sup> expressed the opinion that "the rôle of food in the etiology of many diseases involves increased susceptibility to infection due to lowered resistance caused by faulty diet." Others interested in nutrition have come to the same conclusion, but the work of McCarrison<sup>13</sup> seems to furnish some proof that foods of low vitamin content if used over long periods of time predispose to ulcers and other infections of the gastro-intestinal tract.

The great fault of the American diet is the excessive use of carbohydrates. Sugar saturated, vitamin starved Americans, i e, those who live largely on white flour bread, white potatoes, white rice, white sugar, with which they saturate their coffee, soft drinks and desserts, lean meats, and oleomargarine butter, are prone to ulcer. Therefore, we do not get very far in curing ulcers by feeding the patient devitaminized diets, and we may expect recurrences, if after the patient has had a medical "cure" or a gastro-enterostomy, or resection of the ulcer, he is allowed to go back to the same unbalanced, deficient vitamin diet he was eating when he developed the ulcer.

We have constructed a diet based upon our modification of the original Lenharz diet<sup>14</sup> which is properly balanced and which meets the vitamin requirements of the average malnourished adult ulcer patient. No one diet can be prepared which will suit the needs of every ulcer patient, but this diet, while keeping the vitamin content high, may be added to, or subtracted from, to meet the nutritional requirements of the under-weight or over-weight ulcer patient.

#### *The Relation of Over-Work to Ulcer*

Improper food is surely not the only predisposing cause of ulcer, and a proper diet is not the only consideration in curing the patient. More than twenty years ago, Kauffman<sup>15</sup> called attention to the fact that patients who were in a lowered state of vitality from chronic fatigue were prone to ulcer and likewise were more susceptible to recurrences after treatment. We are convinced that Kauffman is correct in his idea that over-work is a predisposing cause of ulcer. We have had too many ulcer patients who had recurrences both after medical and surgical treatment who gave a history of overwork and long hours, not to have rather strong convictions that rest and prolonged rest, is an important factor in curing the patient, and that if the patient would not have recurrences after treatment, he must regulate his life so that he can have sufficient rest to keep in good physical condition.

Rest bears much the same relationship to the treatment of ulcer that it does in the cure or arrest of tuberculosis and other chronic diseases in

which there is local pathology engrafted on a constitutional condition.

We have noted also that the neurasthenic and psychasthenic element is present in many ulcer cases; and surely the best method of treating psycho-neurasthenia is the Weir-Mitchell rest cure.

#### *Rest In Bed Necessary*

Moynihan<sup>16</sup> asserts that it takes a long time for the gastric or duodenal ulcer to heal. Therefore, he insists that several months in bed is sometimes essential in the medical cure of ulcer, and he believes that fewer cases will come to surgery, if they will take a sufficiently long rest in bed while at the same time receiving the proper diet and medical treatment.

Two months in bed is considered best by many, but we have found that from three to four weeks in bed, with the avoidance of overwork afterwards is usually sufficient to cure the ulcer that can be relieved medically.

The fact that the patient is free from pain does not mean that the ulcer has healed because every surgeon who has had much experience with ulcer knows that when the patient is operated upon in the quiescent stage the ulcer often shows no signs of healing; and many autopsies on persons who never in their lives had ulcer symptoms and who died of other causes, show active ulcers that must have existed for many years. Therefore, the fact that the ulcer patient becomes free from pain in a few days after beginning the diet does not mean that he should not rest in bed for several weeks while undergoing thorough treatment.

*Abstinence From Tobacco Important  
in Curing the Ulcer Patient*

Much has been written by the Germans and the English regarding the use of tobacco as a predisposing cause of ulcer of the stomach and duodenum. Most of the gastro-enterologists of the United States are convinced of the relationship of tobacco to ulcer, though some, notably those who smoke excessively themselves do not believe that tobacco injures anyone in any way at any time.

Sir Berkeley Moynihan<sup>17</sup> recognized as one of the greatest authorities on ulcer in the world does not equivocate in expressing his opinion regarding the influence of tobacco in the pathogenesis of ulcer. In a recent address he said

"Among the most harmful of habits for all these patients is smoking. We have found that in many cases of jejunal ulcer a hyperchlorhydria is present and may be extreme. If a Rehfuß meal is given to a patient accustomed to tobacco at a time when he is not smoking, his normal 'curve' may be recorded, if a second meal is given while a pipe is being smoked, the increase in gastric acidity is very striking. In some cases the excess of free HCL may be slight, but its secretion continues over a long period, in a few cases these two effects of tobacco, increased secretion and increased duration of secretion, are combined. An 'attack' of duodenal ulcer often follows an orgy of tobacco, and many attacks are checked by abstinence from it. 'Attacks' ascribed to duodenal ulcer are sometimes due only to nicotine poisoning, and I have not seldom rescued patients from impending operations by noticing their deeply stained fingers and by prescribing for them a respite from tobacco for a few months and a diminished indulgence in it forever. The close mimicry of hunger-pain in nicotine intoxication appears to have escaped notice."

Moynihan presents charts<sup>18</sup> to illustrate the effects of tobacco on the free acid in the gastric juice. In each test these show a marked increase after smoking.

Tyrrell Gray<sup>19</sup> another British surgeon in discussing tobacco as a predisposing cause of ulcer said

"The predisposing factor in duodenal ulcer is the relative increase of vagus excitation established by diminution of sympathetic control, or by increasing vagus stimulation. There is an outstanding example of an alkaloid which paralyzes sympathetic ganglion cells—that is nicotine. On these grounds I have for some years prohibited smoking in duodenal ulcer."

"The proportion of men to women who have ulcer is roughly four or five to one (in itself perhaps some indication of the influence of nicotine) and 96 percent of the males were smokers. Of the smokers, 22 percent abandoned the habit, or nearly so, with the result that 90 percent were cured, 8 percent greatly relieved, and 2 percent only failed. Where tobacco was unchecked, only 47 percent were cured, and 12 percent recurred. Recurrence is four times as frequent in those who continued smoking."

Eusterman<sup>20</sup> of the Mayo Clinic, in discussing the unfavorable effect of tobacco on ulcer patients says

"The excessive use of tobacco is deleterious to the health of the patient with peptic ulcer. In those susceptible to the influence of nicotine, moderate amounts may be harmful. The patient who craves tobacco invariably consumes excessive amounts and the habit should be discouraged. Langley showed that nicotine paralyzes the synapses of the sympathetic nervous system, so that dyspeptic symptoms in habitual smokers are logical, owing to the unopposed vagal action. Wagner concluded from a recent investigation that all the subjective and roentgenologic signs of duodenal ulcer can be produced by the excessive use of tobacco. During the last decade the typical syndrome of peptic ulcer has been occasionally observed in young



adults given to excessive cigarette smoking, and their discomforts have disappeared largely through the discontinuance of the habit. German clinicians are loath, or refuse, to accept for treatment the patient with peptic ulcer whose fingers are tobacco-stained. I have frequently noticed the peculiar psychologic fact that patients of physicians who are inveterate smokers are not, as a rule, warned to discontinue or restrict the use of tobacco."

"The definitely better end-results that are obtained in either the surgical or non-surgical treatment of ulcer in women should furnish a therapeutic hint and justification for postoperative precautions. While factors of an anatomic, physiologic, and occupational nature may play a part, I feel that such greater success is due more to their wholehearted and continued co-operation regarding matters of diet and mode of eating, and to the fact that generally speaking they are not handicapped by such bad personal habits as the excessive use of tobacco and alcohol.

If tobacco is a predisposing cause of ulcer, it would seem that since smoking among women is becoming almost universal, that one of the by-products of "feminine freedom" will be an increase in the incidence of ulcer among them. It happens that the only case of gastro-jejunal ulcer in a woman that we had last year was that of a movie actress who smoked cigarettes excessively. She had been operated upon six months before she came to us by a surgeon of national reputation and there could not have been any faulty technic in the operation. It was not until she reduced her tobacco that she improved. She never could be induced to give up smoking entirely, and she probably will have a recurrence of her ulcer.

It is difficult to prove that tobacco is a predisposing cause of ulcer, just as it is difficult to prove that an

alcoholic debauch is responsible for some of the perforations in ulcer; yet I and others have observed a number of cases of perforations in ulcer patients after drinking excessively. Still on the authority of such men as Sir Berkely Moynihan, Sir Humphrey Rolleston, Dr Tyrrell Gray, Eusterman and others, it would seem wise to instruct our ulcer patients to discontinue the use of tobacco for the rest of their lives.

### *Curing the Surgical Ulcer Patient*

The mortality following ulcer operations can be reduced and many recurrences prevented by the proper preparation of the patient for the operation and by careful post-operation medical supervision. Marginal or jejunal ulcers, likewise may be prevented if the patient is given the proper instructions regarding diet and hygienic living after operations.

One of the attractions that surgery offered in the past to the ulcer patient was the then current belief of the average layman that after operation for ulcer he could do what he had always been doing and eat what he wants. Many patients who have had recurrences or marginal or jejunal ulcers, or other complications following gastro-enterostomy have become disillusioned about surgery curing ulcer of the stomach in every case, until now many people have a holy dread of an operation for ulcer.

The surgeon themselves are partly to blame for this condition because they often quote a distinguished surgeon who is said to have remarked. "If a man can't eat what he wants after a gastro-enterostomy there is no

use having it done" Probably what he meant was that a man after a gastro-enterostomy can eat all the food he needs, because it would seem that a surgeon would know that a gastro-enterostomy does not remove the cause of an ulcer of the stomach or duodenum; and if the patient in a few weeks after operation goes back to the same eating habits, or the same manner of living which brought on the ulcer, he runs the risk of recurrence of the ulcer, or of the development of a marginal or jejunal ulcer after operation

The practice of surgeons in getting an ulcer patient up two weeks after operation probably accounts for some of the failures in ulcer surgery This is particularly true after a gastro-enterostomy, in which the ulcer is not removed The duodenal ulcer is placed in a favorable condition for healing by a gastro-enterostomy, but an ulcer that has existed for years cannot be expected to heal in two weeks, or even three weeks Therefore three weeks, and in some cases four weeks, in bed following a gastro-enterostomy will give the ulcer patient a better chance for permanent cure than if he is hustled out of the hospital two weeks after his operation. Healing even after clean surgery cannot be said to be complete in two weeks, and at least three weeks rest in bed following ulcer surgery of any kind without doubt is best for the patient

### *Amateur Gastric Surgery*

An important consideration in curing the surgical ulcer patient is the selection of the surgeon, because the immediate mortality and the post

operative complications of gastric operations at the hands of amateur surgeons is something frightful It is perfectly true that many surgeons operating in small hospitals are doing first-class abdominal surgery, but it also is a fact that with the multiplying community hospitals many general practitioners are performing, or rather are attempting to perform, gastro-enterostomies and their faithful patrons are the sufferers from their lack of preparation for doing major surgery

I have not seen any statistics of the results following gastro-enterostomies by general practitioners who do one or two gastro-enterostomies a year, but the study by Verbryck<sup>21</sup> of the end results in gall-bladder surgery in a Washington hospital with an open staff, shows the tragedy of general practitioners attempting to do surgery for which they are not prepared Verbryck showed that in a splendidly equipped Washington hospital that the mortality of one surgeon who performed 62 gall-bladder operations a year was 16 per cent, while the percentage of those who died at the hands of the physicians performing less than ten gall-bladder operations a year averaged 14 per cent In one case of the occasional operator the mortality was 28 per cent

Eusterman<sup>22</sup> in a paper published in 1919 mentions 300 gastro-enterostomies performed by many surgeons in various parts of the country which had to be undone in the Mayo Clinic; and in a study of 84 of their gastro-jejunal ulcers, concludes that they occur in 15 to 2 percent of gastro-enterostomies It perhaps would discourage

the amateur surgeon if it were possible to obtain, and publish, the number of gastro-enterostomy patients who had to be re-operated upon in the United States every year

The physician must let his conscience be his guide as to whether or not he is adequately prepared and the hospital in which he operates properly equipped for gastric surgery, because the lives and future health and happiness of his trusting patients are in his hands.

#### *Dietary Management Before and After Ulcer Operations*

The dietary management of the ulcer patient before operation should be entirely different from that employed in the medical treatment; because the most important problem with the operative ulcer case is to prevent acidosis; and some of the stock diets as advised for the medical treatment of ulcer if used for a few days before operation will surely result in the retention in the body of incompletely metabolized fatty acids, the essential factor in acidosis. It, therefore, is inadvisable to give milk, cream, butter, or other fats to an ulcer patient within 24 hours of operation, but carbohydrates should be given freely, preferably strained orange juice and ten percent solution of dextrose, corn syrup, or honey

The time required to properly prepare an ulcer patient for operation varies greatly, and depends to a great extent upon his state of nutrition. The well nourished ulcer patient may be prepared for operation in one or two days, but the emaciated, anemic, debilitated ulcer patient, who is de-

hydrated and has no vitality will stand a better chance for recovery after operation if he can be placed in a better state of nutrition. Certainly no patient with gastric retention should be operated upon without a thorough study of kidney function. If the blood urea, or the non-protein nitrogen is high, the patient should be given only liquids, largely soluble carbohydrates until the kidneys are functioning normally

Sir Berkley Moynihan stresses particularly the preparation of ulcer patients for operation, stating that it often requires weeks to get them prepared.

The dietary after care of ulcer operative cases is also most important. No fats should be given in three or four days after operation and not then if the patient is vomiting or shows other symptoms of acidosis. Likewise the stock diets have no place in the dietary management of ulcer patients within two weeks after operation

The prevailing custom among surgeons of allowing ulcer patients to go on a general diet, "eat what you want," two weeks after a gastro-enterostomy, or other operation for ulcer, is responsible for the failure to cure many patients. On questioning most of the ulcer patients who were not relieved by surgery, or who had recurrences, or marginal ulcers, and who came to us for medical treatment, they almost invariably said that their surgeons had told them they could "eat what they wanted two weeks after operation," and few of them remembered having been given any instructions whatever regarding diet, or personal

hygiene, during the time of their convalescence after their operations. It may be added that a number of these patients had been operated upon by surgeons of great reputation.

When surgeons consider the pathology of gastric or duodenal ulcers, they must know that healing cannot take place in two weeks. They also should realize that there is more to surgery than the mere mechanics of an operation, that the surgeon's obligation to his patient does not end when the wound he has made has healed. Certainly surgeons will have better results following gastric surgery if they are more careful in dieting their patients after operation. They should inform their patients that it takes an ulcer a long time to heal after a gastro-enterostomy, and that the original cause of the ulcer has not been removed by operation, and that if he would not have a recurrence he must be careful about his diet for six months or a year after he leaves the hospital. What is still better, surgeons, when possible, should have the cooperation of physicians of ample experience in the dietary management of their ulcer patients. They should also follow up such patients for from six months to a year to see that they carry out the proper diet.

#### *System of Hygienic Living for Ulcer Patients*

The great majority of properly treated ulcer patients, whether medical or surgical, may look forward to becoming more efficient and to enjoying life more than they ever did before, provided they follow the same rules of personal hygiene that every man in

health should observe. The ulcer patient perhaps will live longer than he would have had he not developed an ulcer, because if taught properly how to live, as the physician or surgeon has the opportunity of doing, he will take such good care of himself that he will be less susceptible to many of the infirmities of middle life, and old age will thus be deferred.

A copy of the following outline of a system of hygienic living with copies of simplified diet lists prepared to suit his particular needs is given to each of our ulcer patients before they are dismissed.

1 THE PROPER DIET—Three medium meals a day at the same hours, and a glass of milk between meals for at least three months after treatment; then one raw fruit, one raw vegetable, two cooked tender green vegetables, a pint to a quart of milk every day for the rest of his life. Meat and light desserts, not more than once a day. Enough bread, potatoes, rice, butter and other simple foods to maintain the normal weight. Thorough mastication of food is most important.

2 WORK—AVOID OVERWORK—Six to eight hours of honest work a day for five days a week and three or four hours on Saturday.

3 SLEEP—Eight or nine hours in bed at night, and lie down, sleep, if possible, for half an hour after the noon meal.

4 EXERCISE—Fifteen minutes room exercises with windows wide open, before the morning bath. Follow the bath with massage (brisk rubbing with open hand) of the entire body until the skin is reddened. A

walk of one or two miles in the open air and sunlight each day, or what is better, play golf two or three afternoons a week.

5. RECREATION—Eight hours for play includes morning exercises, bath, golf, or other outdoor exercises; time for eating at least  $\frac{1}{2}$  hour for each meal, perhaps an hour for dinner and no work or serious reading after six o'clock in the afternoon. Frequent week-end trips and an annual vacation of from two weeks to a month every year.

6 SERENITY—Worry, anger, grief, abnormal fears, or other emotional disturbances will break down resistance to infections. Therefore, the cured ulcer patient should cultivate serenity in all the relations of life.

7. ELIMINATE THE TOXINS—Coffee, tea and the so-called Cola drinks, which contain caffeine, a habit forming drug, should not be used by the ulcer patient, except occasionally as a stimulant after losing sleep, or as a drug for headache or shock. Tobacco and alcohol are predisposing causes of ulcer and are quite injurious to the ulcer patient. Therefore, he

should never use them in any quantity, even after his ulcer has been pronounced cured.

8. THE ANNUAL OR SEMI-ANNUAL PHYSICAL EXAMINATION—Every adult should have an annual, or semi-annual, physical examination even when in health. The ulcer patient should report to his physician once a month for six months, and then for the rest of his life have an annual or semi-annual physical examination, with particular reference to a possible return of the ulcer; or the possible development of a cancer of the stomach, which, if diagnosed early, can be cured by operation.

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Each section of the above outline of hygienic living is discussed with the patient and he is shown how he can conform his daily habits to a regular systematic regimen. He is also impressed with the fact that his future health, efficiency and happiness depend largely upon his living the simple hygienic life, that he must do his part in preventing a recurrence of his ulcer.

TABLE I    ULCER DIET FOR THE FIRST WEEK OF TREATMENT

<i>Amount</i> Table-			FOOD
Gm	Oz	spoonsful	
			<i>First Day</i>
15	$\frac{1}{2}$	1	Every hour from 7 a m to 7 p m, $\frac{1}{2}$ ounce of a mixture of $2\frac{1}{2}$ ounces of cream to 4 ounces of milk (thirteen feedings)
15	$\frac{1}{2}$	1	Strained orange juice after the milk and cream at 7 a m, 1 p m and 7 p m
			<i>Second Day</i>
30	1	2	Every hour from 7 a m to 7 p m, 1 ounce of a mixture of 4 ounces of cream and 9 ounces of milk (thirteen feedings)
30	1	2	Strained orange juice after the milk and cream at 7 a m, 1 p m and 7 p m
			<i>Third Day</i>
45	$1\frac{1}{2}$	3	Every hour from 7 a m to 7 p m (inclusive), $1\frac{1}{2}$ ounces of a mixture of $7\frac{1}{2}$ ounces of cream and 12 ounces of milk (thirteen feedings)
45	$1\frac{1}{2}$	3	Strained orange juice after the milk and cream at 7 a m, 1 p m and 7 p m
			<i>Fourth Day</i>
60	2	4	Every hour from 7 a m to 7 p m (inclusive), 2 ounces of a mixture of 8 ounces of cream and 18 ounces of milk (thirteen feedings)
60	2	4	Strained orange juice after the milk and cream at 7 a m, 1 p m and 7 p m
			<i>Fifth Day</i>
75	$2\frac{1}{2}$	5	Every hour from 7 a m to 7 p m (inclusive), $2\frac{1}{2}$ ounces of a mixture of $12\frac{1}{2}$ ounces of cream and 20 ounces of milk (thirteen feedings)
60	2	4	Strained orange after the 7 a m, 1 p m and 7 p m feedings of milk and cream
			<i>Sixth Day</i>
90	3	6	Every hour from 7 a m to 7 p m (inclusive), 3 ounces of a mixture of 15 ounces of cream and 24 ounces of milk (thirteen feedings)
60	2	4	Strained orange after the 7 a m, 1 p m and 7 p m feedings of milk and cream mixture

TABLE 2    ULCER DIET FOR THE SECOND WEEK OF TREATMENT.

			<i>Seventh to Tenth Days</i>
Gm	Oz	Amount Table- spoonfuls	
90	3	6	8 A M BREAKFAST
90	3	6	Strained orange juice
			Strained oatmeal or one shredded wheat biscuit, toasted, or 1 slice dry toast of whole wheat bread
90	3	6	Milk
			One soft boiled egg
10	1	1	Pat butter
60	2	4	Cream
			10 AND 11 A M
90	3	6	1 ounce of cream and 2 ounces of milk
			1 P M DINNER
90	3	6	Strained tomato juice
25	1	1 large	Scraped beef, lightly broiled
90	3		Milk
30		(1 slice)	Whole wheat bread, toasted
			3 AND 5 P M
90	3	6	1 ounce of cream and 1 ounce of milk
			6 P M , SUPPER
90	3	6	Strained orange juice
90	3	6	Strained oatmeal or one shredded wheat bis-
20			cuit, toasted, 1 thin slice dry toast of whole wheat bread
60	2	4	Cream
			One soft boiled egg
			One pat butter
90	3	6	Milk
			9 P M
90	3	6	2 ounces of milk and one ounce of cream

TABLE 3 ULCER DIET FOR THE ELEVENTH TO FOURTEENTH DAYS

Gm	Oz	Amount Table- spoonsful	
8 A.M., BREAKFAST			
90	3	6	Orange juice (strained)
90	3	6	Strained oatmeal or one shredded wheat biscuit
90	3	6	Cream
			One soft boiled egg
30		(1 slice)	Whole wheat bread, toasted
10		(1 pat)	Butter
10 A.M.			
120	4	8	Milk
11 A.M.			
120	4	8	Milk
1 P.M., DINNER			
90	3	3	Strained tomato juice
50	2	2 large	Scraped beef or minced breast of chicken
30		(1 slice)	Dry toast, whole wheat
10		(1 pat)	Butter
60	2	2	Ice cream
3 P.M.			
120	4	8	Milk
5 P.M.			
120	4	8	Milk
6 P.M., SUPPER			
90	3	6	Orange juice, (strained)
			One soft boiled egg
30		(1 slice)	Whole wheat bread, toasted
10		(1 pat)	Butter
9 P.M.			
120	4		Milk



TABLE 4. ULCER DIET FOR THIRD WEEK OF TREATMENT

			<i>Fifteenth Day to Twenty-first Day</i>
Gm.	Oz	<i>Amount</i> Table- spoonsful	
			8 A M., BREAKFAST
90	3	6	Strained orange juice or strained grapefruit juice
90	3	6	Strained oatmeal
90	3	6	Cream
			Two soft boiled eggs
30		(1 slice)	Toast, whole wheat bread
10		(1 pat)	Butter
150	5	10	Glass of milk
			11 A.M
150	5	10	Glass of milk
			1 P M , DINNER
120	4	8	Strained tomato juice or strained vegetable soup
100	4	4 large	Scraped beef or minced breast of chicken
100		4	Tender green vegetables, as turnip greens, spinach or string beans (mashed through sieve)
30		(1 slice)	Toast, whole wheat bread
20		(2 pats)	Butter
120	4	4	Ice cream, cup custard, boiled custard or gelatin and cream
			4 P M
120	5	10	Glass of milk
			6 P M , SUPPER
120		8	Thick puree of peas or beans
100		4	Tender green vegetables, as turnip greens, spinach or string beans mashed through sieve
30		(1 slice)	Toast, whole wheat bread
20		(2 pats)	Butter
150	5	10	Glass of milk
90	3		Strained orange juice
			9 P M
150	5	10	Glass of milk

TABLE 5 ULCER DIET FOR FOURTH, FIFTH AND SIXTH WEEKS OF TREATMENT

Gm	Oz	Amount spoonfuls Table-	<i>Fourth to Sixth Weeks</i>
8 A M , BREAKFAST			
90	3	6	Strained orange juice
90	3	6	Strained oatmeal, or $\frac{1}{2}$ shredded wheat biscuit
90	3	6	Cream
			One egg, soft boiled, poached or scrambled
60		(1 slice)	Dry toast, whole wheat bread
20		(2 pats)	Butter
10 A M			
150	5	10	Milk
1 P M , DINNER			
120	4	8	Strained tomato juice, clear broth or tomato broth, or strained vegetable soup
100	4	4 large	Scraped beef or minced chicken or lamb
100		4	Turnip greens, spinach or string beans, mashed through a sieve
60		(1 slice)	Dry toast, whole wheat bread
20		(2 pats)	Butter
120	4	4	Ice cream, boiled custard or gelatin, or water- melon or cantaloup juice
4 P M			
150	5	10	Glass of milk
6 P M , SUPPER			
120	4		Thick puree of peas or beans
90		3	Turnip greens, spinach or string beans, mashed through a sieve
60		(1 slice)	Dry toast, whole wheat bread
20		(2 pats)	Butter
120	4	8	Milk
120	4	8	Strained orange juice
9 P M			
150	5	10	Glass of milk

TABLE 6 ULCER DIET AFTER SIX WEEKS

## BREAKFAST

*One fruit* Strained orange or grapefruit juice

*One Cereal* Small portion of thoroughly cooked oatmeal, or 1 shredded wheat biscuit with  $\frac{1}{2}$  glass cream—no sugar

*Eggs* 1 or 2 eggs poached or soft boiled, or soft scrambled

*Bread* 1 slice whole wheat bread, 2 or 3 pats butter, 2 tablespoonful honey

*Milk* 1 glass sweet milk

*Three hours after breakfast take glass milk (one-third cream)*

## DINNER

*Soup* Strained chicken, celery, vegetable, barley soup, or strained tomato juice

*Tender Meats* (Small portion) Broiled, boiled, or baked—not fried Small portion of chicken, turkey, mutton, roast beef, bacon, thinly sliced boiled ham, or fish

*Tender green vegetables* (one or two varieties) Large serving spinach, turnip greens, tender beans, cooked without much grease Butter or mayonnaise or olive oil and lemon juice may be used freely on vegetables after they have been cooked

*Bread* One slice whole wheat bread or dry toast or small piece of country ground corn meal bread, or 1 small corn muffin, two or three pats of butter.

*Milk* 1 glass sweet milk, or buttermilk, (one third cream)

*Dessert* Soft part of baked apple, thoroughly ripe banana, or other fruit with cream—no sugar Ice cream, or gelatin, or sherbet twice a week

*Three hours after dinner take glass of milk (one-third cream)*

## SUPPER

*Soup* Puree (thick strained soup) of peas or beans, or oyster stew—no oysters

*Tender green vegetables* \*Large serving of spinach, turnip greens, mustard greens, tender string beans, cooked without much grease.

*Bread* 1 slice whole wheat bread or dry toast 2 or 3 pats butter

*Milk.* 1 glass sweet milk, or buttermilk (one third cream)

*Dessert.* Strained orange juice, soft part baked apple, or very ripe banana and cream without sugar, or gelatin, or egg custard

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# Unusual Addison's Syndromes\*†

By A. B. BROWER, M.D., F.A.C.P., *Dayton, Ohio*

“THE leading and characteristic features of the morbid state to which I would direct attention are anemia, general languor and debility, remarkable feebleness of heart action, irritability of the stomach, and a peculiar change in color of the skin occurring in connection with diseased condition of the suprarenal capsule.” This original description of adrenal insufficiency by Addison<sup>1</sup> remains classical

If a patient presents these clinical phenomena and at autopsy shows bilateral destructive changes of the adrenals, there can be no doubt as to the diagnosis. On the other hand, if a patient presents the clinical manifestations of Addison's disease, and at autopsy no abnormalities of the adrenals are revealed, it is usually assumed that there has been destruction and impairment of function of the chromaffine system outside of the adrenals. Addison described a clinical and not a pathological concept.

What are the functions of the adrenal glands? The gland is composed of two distinct layers—the medulla and cortex. The medullary portion is composed largely of chromophil cells

of central nervous system origin. This portion is not essential to life, but is the source of the only known active principle—epinephrin. It is generally assumed that the hormone enters the circulation by way of the central veins of the gland. This secretion has a pronounced effect on the functions of structures innervated by the sympathetic nervous system. The cortex is composed of epithelial areas derived from the wolffian body. This portion is essential to life. It is generally accepted that the cortex furnishes a substance affecting growth and reproduction; attempts to isolate the vital hormone have not met with success. It might be well to mention that the complete Addison's syndrome has never been produced experimentally.

The pathological conditions of the adrenals most often found at autopsies performed on patients showing the typical Addison's syndrome are tuberculosis, syphilis and malignancy, in rare instances, pressure atrophy, lymphadenoma, mycosis fungoides, infarcts in children, roentgen ray necrosis, or hypoplasia is encountered.

In a recent survey made by Barker<sup>2</sup> of the Mayo Clinic, of twenty-eight cases of Addison's disease which came to autopsy, the following was found. In twenty-five of the cases advanced bilateral tuberculosis of adrenals was

\*From the Diagnostic Division of the Dayton Clinic, Dayton, Ohio

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demonstrated, in three, bilateral atrophy was found; in eleven of fourteen cases autopsied in the last four years, an acid-fast bacillus resembling the tubercle bacillus was found in the sections of the gland. In twenty-five cases, healed tuberculosis was found in the lungs. In thirteen cases, tuberculosis was active in the lungs. In six cases, active tuberculosis was found in the genito-urinary organs, while in three instances, active tuberculosis was found in the lymph glands, spleen, and liver. In only three cases was there no evidence of active tuberculosis in the adrenals. In this series, there was one case of syphilis of the adrenals. That syphilitic adrenalitis may be a more frequent etiological factor in the development of Addison's disease than is generally believed is indicated by the recent studies of Warthin.<sup>8</sup> The writer has observed the development of many of the symptoms of Addison's disease after influenza infections and after severe stress and strain, as was experienced during the World War, in these cases these symptoms were transitory.

The cause of the pigmentation in Addison's disease has given rise to much investigation and conjecture. According to Loeper<sup>4</sup> the etiological factors fall into four groups: adrenal origin, cachectic, nervous, and mixed origin. Most investigators believe that both the adrenal glands and the sympathetic nervous system are factors. Lowered suprarenal secretion lessens the ability of the tissues to eliminate sulphur. The high sulphur content of the blood in the presence of melanoderma suggests that this is an important factor in the production of excessive melanin pigmentation. Brit-

torf<sup>5</sup> suggests that the increase of oxidase in the skin plays an important rôle.

Addison's disease manifests itself in four distinct forms, gastro-intestinal, painful, melanodermic, and asthenic. In the painful and melanodermic types, the involvement of the sympathetic system appears to dominate the clinical picture. In the asthenic type, the adrenal insufficiency is most pronounced. In analysing such a classification we discover the outstanding symptoms as described by Addison. The four most common clinical characteristics are asthenia, pigmentation, gastro-intestinal disturbance, and hypotension. At least three of these symptoms are necessary to make a diagnosis. Anorexia, nausea, vomiting, gaseous eructation, and meteorism are common complaints. Alternating attacks of constipation and diarrhea are frequent symptoms. Loss of weight is quite constant. Patients often experience lumbar and abdominal pains, and, in some cases, anginal pains occur, despite the presence of hypotension. Dyspnea is more likely to be a terminal condition and is frequently associated with syncope and collapse, due to feeble heart action and extreme terminal hypotension. The heart sounds are weak. The presence of hypotension is not essential to a diagnosis of Addison's disease, since a systolic pressure of 120 or above has been reported in a number of cases. However, the majority of patients have a systolic blood pressure below 100. A study of the literature reveals that pigmentation is rarely absent. In these cases in which melanoderma is absent, it is difficult to establish a diagnosis of

Addison's disease. Melanosis usually occurs more distinctly on exposed areas and on approximating surfaces. All mucous membranes are usually pigmented, especially the lips

The laboratory investigations in this disease have yielded important data. Contrary to Addison's statement, anemia is not a cardinal feature. The vast majority of cases show a marked lymphocytosis. Blood sugar values usually fall within normal limits. According to Brown,<sup>8</sup> of the Mayo Clinic, the circulating blood and plasma were normal in all cases. Electrocardiographic tracings show no abnormalities characteristic of this disease. Urine analysis usually shows a normal output with a slight amount of albumin and a few hyaline and finely granular casts. Some observers have found that as many as 40 per cent of their patients with Addison's disease showed glycosuria. This has not been our experience, nor have the investigators at the Mayo Clinic found this to be true. Lowered renal function seems to be the rule, which is rather to be expected in view of the marked circulatory asthenia. No appreciable disturbance of hepatic function has been demonstrated. Lowered gastric acidity or complete achlorhydria is the rule. A lowered basal metabolism rate was found in thirty-three per cent of the cases in which metabolic determinations were made.

In the differential diagnosis of Addison's disease, those conditions in which diffuse cutaneous pigmentation is a cardinal sign should be carefully considered. In pernicious anemia, the skin has a lemon tint as opposed to the brownish discoloration in Addison's

disease; the blood picture will aid in the solution of this problem. In malignancy, we find more wasting and the discovery of the neoplasm will clear the diagnosis. Arsenic poisoning will frequently give a similar skin color; here we find the history, lack of mucous membrane pigmentation, and the presence of hyperkeratosis helpful in establishing the diagnosis. The Marsh test of the urine, before and after giving sodium thiosulphate, will often be of value in such cases. Pregnancy occasionally causes marked increase in pigmentation, but in these cases the muscular and vascular asthenia is not so great; the history and vaginal examination will give the correct diagnosis. Various liver conditions give rise to color changes in the skin; the change in the size of the liver, the icterus index, hepatic function tests, the presence or absence of bilirubinuria, and acholic stools will aid in the differentiation. Hemachromatosis gives a distinct pigmentation, the presence of hypertrophic cirrhosis, glycosuria, and histologic examination of the skin for hemosiderin deposits will establish this diagnosis. Malarial pigmentation does not affect the mucous membranes and the finding of the plasmodia makes this diagnosis definite. Patients with pulmonary tuberculosis occasionally will show skin pigmentation, but the chest findings and the degree of asthenia are of value in differentiating this condition from Addison's disease. It must be borne in mind, however, that active pulmonary tuberculosis and Addison's disease will be often found in the same patient. The history of the case and the bluish-gray pigmentation are the important

considerations in algyria. Dementia, delirium, diarrhea, and the restriction of pigmentation to exposed areas are the cardinal signs and symptoms in pellagra. The pigmentation occasionally associated with Graves' disease is to be distinguished by hypertension, rapid and strong heart action, palpable thyroid, and the increased metabolic rate. The occasional pigmentation in lues can be identified by the history, lack of hypotension and asthenia, and by the Wassermann and Kahn reactions. The degree of fatigability of a muscle can be studied by ergography and is more pronounced in Addison's disease.

Two cases have been encountered recently, which, although presenting the typical clinical symptoms described by Addison, showed at autopsy pathological conditions which are very unusual.

*Case 1.* A single girl, twenty-eight years old, was referred to us by a surgeon whom she consulted relative to the advisability of having her thyroid gland removed. She complained of asthenia, pigmentation, rapid heart, nervousness, and pains through her chest and back. Her mother was living but had pernicious anemia. Her father was living and well. She had four brothers and three sisters all in good health. Her babyhood, childhood, and adolescence were uneventful. The only acute infectious disease was influenza during 1917. There was no history of venereal disease, surgical operations, or serious injuries. She never used tea, coffee, tobacco, or alcohol.

Her maximum weight was 145 pounds, the present weight was 109 pounds. The patient said she had not been well for three years. She had been treated for bronchitis and liver trouble, and for the past year had been under treatment for goiter. During this time she had gradually grown worse. Since the onset of illness she experienced the following symptoms: many headaches, far-sightedness, frequent colds with cough

some enlargement of the thyroid gland, and indigestion. During the development of these symptoms, she observed a change in the color of her skin, but thought and was told that she was jaundiced. She experienced constipation and generalized pain involving the joints, back and chest. For the past year she had a rapid heart, nervousness, and some loss of weight.

Physical examination showed a tall, thin girl, with a yellowish-brown skin. The buccal and vaginal mucous membranes showed a similar brownish pigmentation. The temperature was 97, pulse 84, respiration 18. The pupils reacted to light and in accommodation. The retinae showed no pigmentation. The ears and nose were negative. The tonsils were moderately infected. The teeth showed moderate pyorrhea. Moderate general lymphadenopathy was found. The thyroid was palpable, soft, moderately enlarged, and somewhat tender. The breasts were negative. The heart showed no deviation from the normal. A few râles were heard over the right hilus. The liver, spleen and kidneys were normal in size and position. The pelvic examination was negative. The nervous system showed nothing unusual. The urine was acid, specific gravity 1.021, otherwise negative. The blood examination showed hemoglobin 68 per cent, red blood cell count, 4,800,000, white blood cell count, 5,900, polymorphonuclears, 46 per cent, large lymphocytes, 13 per cent, small lymphocytes, 41 per cent. The Wassermann and Kahn reactions were negative. The blood pressure was 115/88. The metabolic rate was minus 2. The Vandenberg reaction was negative and the icterus index was 5. The blood sugar was .09 mgm per 100 cc. X-ray findings of the chest were negative.

The patient worked as a stenographer up to three weeks before coming to my office. On account of the marked asthenia she was moved to the hospital. Here the asthenia rapidly grew worse, dyspnea developed and the patient died five days after admission to the hospital.

The pertinent findings at the post-mortem examination, performed by Dr. Walter M. Simpson, Pathologist, Miami Valley Hospital, follow. The body was that of



a fairly well developed adult white woman. The skin showed diffuse deep brownish pigmentation with multiple scattered, more deeply pigmented areas, averaging pinhead size. The pigmentation was most marked in the axillae and perineum. The sclerae showed no pigmentation. There was slight, soft, symmetrical enlargement of the thyroid gland. The mucous membranes showed marked pallor with diffuse brownish pigmentation, less marked than in the skin.

Because of stated restrictions the brain was not examined.

The thymus showed marked hyperplasia, measured 8 x 6 x 13 cm, and weighed 38 grams, on section, there was no evidence of fatty atrophy (see fig 1). The heart was much smaller than the cadaver's right fist. The aortic orifice barely admitted the tip of the thumb. The lungs were negative save for intense acute passive congestion and

scattered areas of healed tuberculosis. Multiple healed tubercles were found in the bronchial nodes. The thoracic aorta showed marked hypoplasia. The thyroid gland showed an excess of colloid.

The spleen was approximately twice normal size, it weighed 319 grams, on section, there was a marked increase in the size and number of the Malpighian corpuscles. There was a marked increase in the number and size of the solitary lymph follicles of the intestinal tract, the Peyer's patches of the small intestine showed marked lymphoid hyperplasia. The mesenteric and retroperitoneal lymphnodes showed distinct hyperplasia, varying in size from kidney bean to cherry.

The left adrenal was found after considerable search in the renal fatty capsule, it was greatly reduced in size and on section showed no grossly visible medullary tissue,

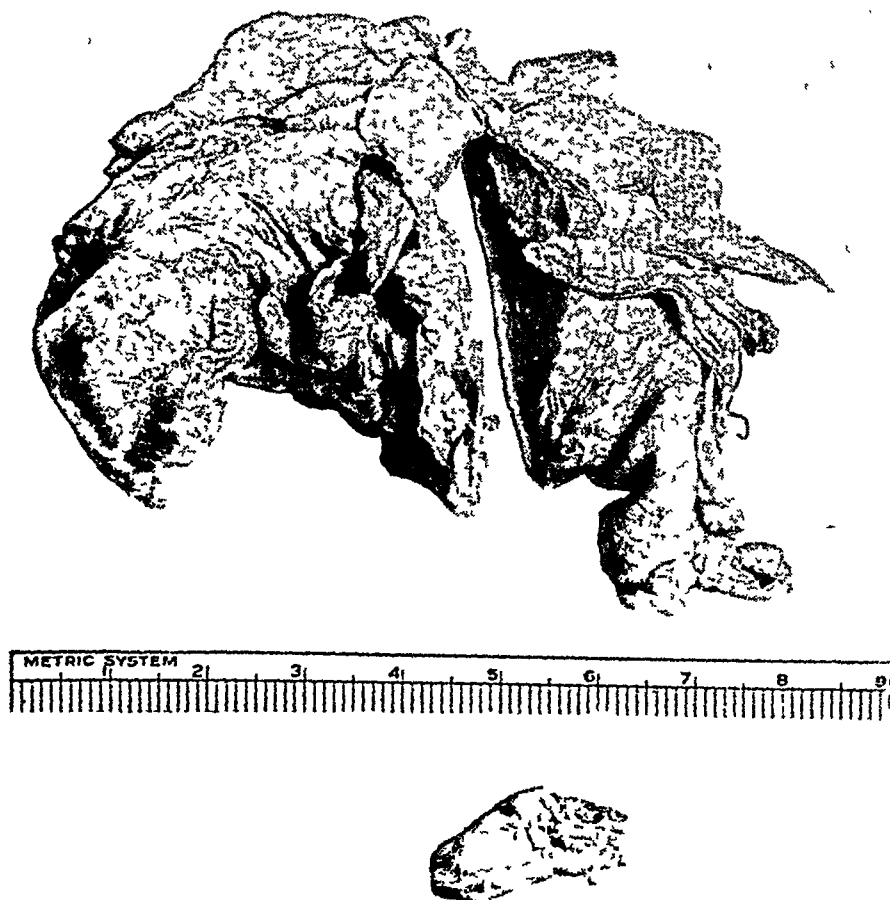


FIG 1 Case 1 Persistent hyperplastic thymus and markedly hypoplastic left adrenal

it measured 2.2x1.0x0.4 cm (see fig 1). Careful dissection failed to reveal the presence of a right adrenal, the tissue in the right adrenal region was saved for microscopic examination, in the hope of finding some evidence of adrenal tissue. The kidneys were of normal size, the fibrous capsule stripped readily and on section revealed only the deeply congested surface. The uterus showed marked hypoplasia, the other pelvic structures showed no abnormalities.

Microscopic examination of the hypoplastic right adrenal showed normal relationship of the cells of the three cortical zones, only a few medullary cells could be seen, there was no evidence of any inflammatory process. Careful microscopic examination of the tissue from the right adrenal region showed no evidence of adrenal tissue. The thymus showed abundant thymic tissue with many well-preserved corporcles of Hassall. The thyroid tissue showed an excess of colloid, the acini were lined by a single layer of flat epithelial cells, there was extensive lymphoid hyperplasia of the thyroid tissue with many well-defined germ centers. Sections of the skin and vaginal mucous membrane showed an excess of melanin pigment in the basal layers of the epidermis.

*Pathological diagnosis* Agnesia of right adrenal, extreme hypoplasia of the left adrenal. Persistent hyperplastic thymus. Generalized lymphoid hyperplasia. Marked hypoplasia of the aorta and heart. Status thymicolymphaticus. Diffuse melanosis of skin and mucous membranes. Terminal right sided cardiac dilatation with relative tricuspid and pulmonary insufficiency. Intense acute passive congestion of all organs. Healed tuberculosis of lungs and bronchial lymph nodes. Hypoplasia of uterus.

*Case 2* A fifty-eight year old white woman was admitted to the Medical Service of the Miami Valley Hospital in a state of orthopnea. She gave as her chief complaints shortness of breath and anemia. She

stated that she had been treated for some type of anemia for many weeks and had been sent to the hospital for transfusion. She said she was fairly well until four months before presenting herself at the hospital, at which time she first experienced difficulty in breathing, associated with marked weakness. Some difference in the color of her skin was noted, but no significance was attributed to it. The dyspnea increased and the patient was confined to her bed for only two days before coming to the hospital. She had experienced frequent urination, constipation, and sharp pains in the lower extremities. She was well developed but poorly nourished. A general melanosis was noted, especially emphasized on the exposed areas and approximating surfaces. The mucous membranes of the mouth and vagina showed similar melanosis. The respirations were deep and slow—eight to twelve per minute. The pupils reacted normally to light and in accommodation. The sclerae were clear. The few remaining teeth showed marked caries. The throat showed no marked inflammation. The tongue was rough and dry. There was no palpable cervical adenopathy. No evidence of active tuberculosis was found in either lung. The heart was small, the cardiac rate and rhythm were normal, a systolic bruit was heard at the apex. The blood pressure was 100-65. The liver and spleen were not palpable. An irregular nodular mass was outlined in both flanks in the position in which one would expect to find a ptotic kidney. There was no edema of the extremities. The pelvic and rectal examinations were negative, except for the presence of a small polypus which extruded from the cervical canal. The tendon reflexes were prompt and equal.

On entrance to the hospital, the patient had a temperature of 98.8° F, pulse 130. She lived but three days after entering the hospital, and during this time voided but twelve ounces of urine. This was acid in reaction, the specific gravity was 1.015, there was trace of albumin, a few pus cells and an occasional hyaline cast. The blood examination showed hemoglobin of 80 per cent, red blood cells, 3,340,000, white blood cells, 28,150, and a relatively low lymph-

ocytosis The Wassermann and Kahn reactions were negative The blood chemical analysis showed creatinine content of 15 mgm per 100 cc, urea nitrogen 60, urea 128, and blood sugar 143 These greatly increased nitrogenous values were coincident with marked asthenia, increased melanin pigmentation, dyspnea, constipation, and hypotension A diagnosis of adrenal insufficiency was made, probably due to the pressure exerted upon the adrenals by the two masses found in either flank, or to neoplastic invasion of the adrenals A further diagnosis of renal insufficiency was made on the basis of the blood chemical analysis

The following abstract of the autopsy findings is taken from the report of the autopsy performed by Dr Walter M Simpson The body was that of a tall slender white adult female The skin was fine, soft and elastic and showed diffuse melanosis, most marked over the exposed areas, axillae and perineum The mucous membranes showed approximately the same degree of melanosis as the skin There was early cataract of the left lens, the sclerae were clear The brain and spinal cord presented no noteworthy changes The examination of the thoracic viscera revealed no abnormalities, except a moderate degree of aortic atherosclerosis and healed pulmonary and bronchial node tuberculosis, there was no grossly visible thymic tissue, the aorta presented no evidence of syphilis

The liver was about two-thirds normal size, weighed 1100 grams and measured 22 x 16 x 15 cm Through the capsule could be seen multiple thin walled cysts, many of which were elevated above the surface of the liver, these varied in size from pin-head to cherry and were filled with clear fluid On section numerous similar cysts were found throughout the substance of the liver (see fig 2) Otherwise the liver presented no abnormalities, except moderate cloudy swelling and chronic passive congestion The left kidney was enormously enlarged, measuring 19 x 10 x 7.5 cm (see fig 3) The renal surface was very irregular due to the presence of thin walled cysts varying in size from small pea to walnut On section, the entire kidney was seen to be made up of similar cysts, with small scat-

tered islands of interposed renal parenchyma The pelvis was thin walled and showed slight dilatation The right kidney was slightly smaller but presented the same gross characteristics The left adrenal showed marked pressure atrophy, being about one-third the normal size, it weighed 18 grams and measured 3 x 1.5 x 0.3 cm The right adrenal showed practically the same degree of pressure atrophy, it weighed 2 grams and measured 3.2 x 1.4 x 0.4 cm On section, the adrenals showed the normal relationship between cortex and medulla

Microscopic studies of sections of the skin and vaginal mucous membrane showed a marked increase of melanin pigment Sections of the liver showed multiple monolocular cysts lined by a single layer of flat epithelial cells, the liver cells showed patchy fatty degenerative infiltration with marked diffuse cloudy swelling and passive congestion The adrenals showed marked atrophy of both cortex and medulla, there were no inflammatory infiltrations The kidneys showed multiple large cysts lined by cuboidal epithelial cells, the glomeruli and tubules were widely separated by connective tissue, much of which was hyalinized and showed patchy lymphocytic infiltrations, there were numerous scarred glomeruli and multiple hyaline casts in the collecting tubules

*Pathological Diagnosis* Bilateral congenital polycystic kidneys Renal insufficiency Pressure atrophy of adrenals Congenital polycystic liver Diffuse melanosis of skin and mucous membranes Moderately advanced aortic atherosclerosis Healed pulmonary and bronchial node tuberculosis Simple atrophy of pancreas Polypoid glandular hyperplasia of endometrium Multiple uterine fibromyomata Cachexia

#### DISCUSSION

An interesting observation in the first case is that the patient was treated for one year for hyperthyroidism, although the blood pressure was 115/88



FIG 2 Case II Cut surface of polycystic liver, with many monolocular thin walled cysts, varying in size from pin-head to cherry, and filled with clear fluid

and the metabolic rate was minus 2. The irritability of the heart, nervousness, and loss of weight were probably misleading. A prominent symptom in this case, common to many cases of Addison's disease, but rarely thought of as an important part of the clinical syndrome, was the marked back and chest pain. Early in the course of the disease, a diagnosis of catarrhal jaundice was made, but this was dismissed from consideration on the basis of the Vandenberg test, icterus in-

dex, and absence of bile in the urine. A clinical diagnosis of Addison's disease was made because of the presence of marked asthenia, typical pigmentation and gastro-intestinal disturbances. The most striking pathological considerations in this case are concerned with the constitutional abnormalities. Hypoplasia of the adrenals is a common finding in status thymicolymphaticus, in this case however, the agenesis and hypoplasia far exceeded that ordinarily observed in this diathesis.

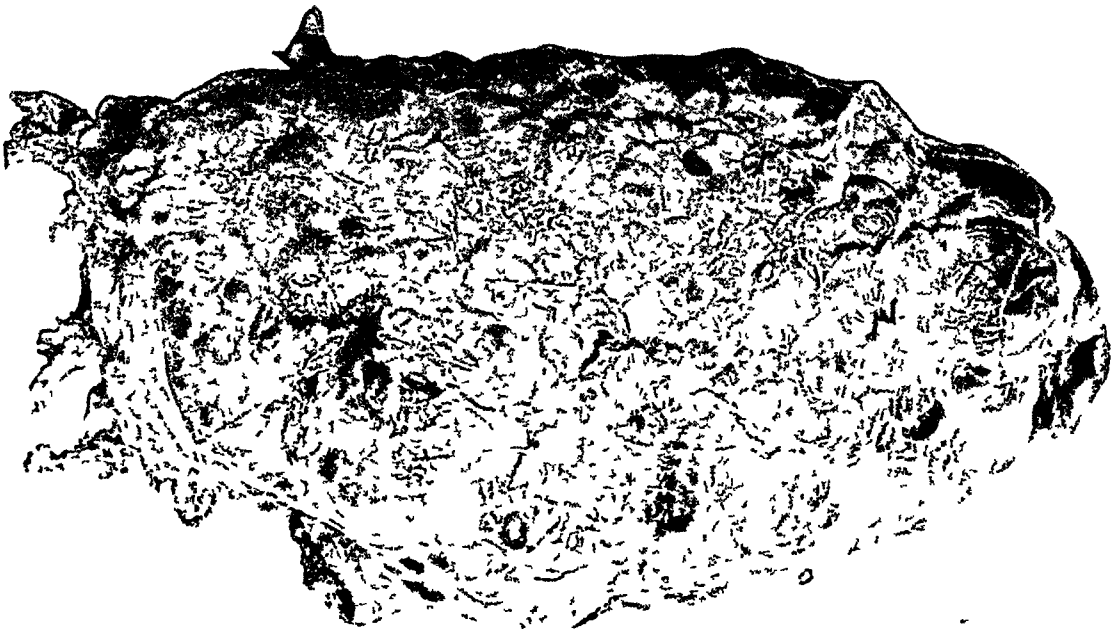
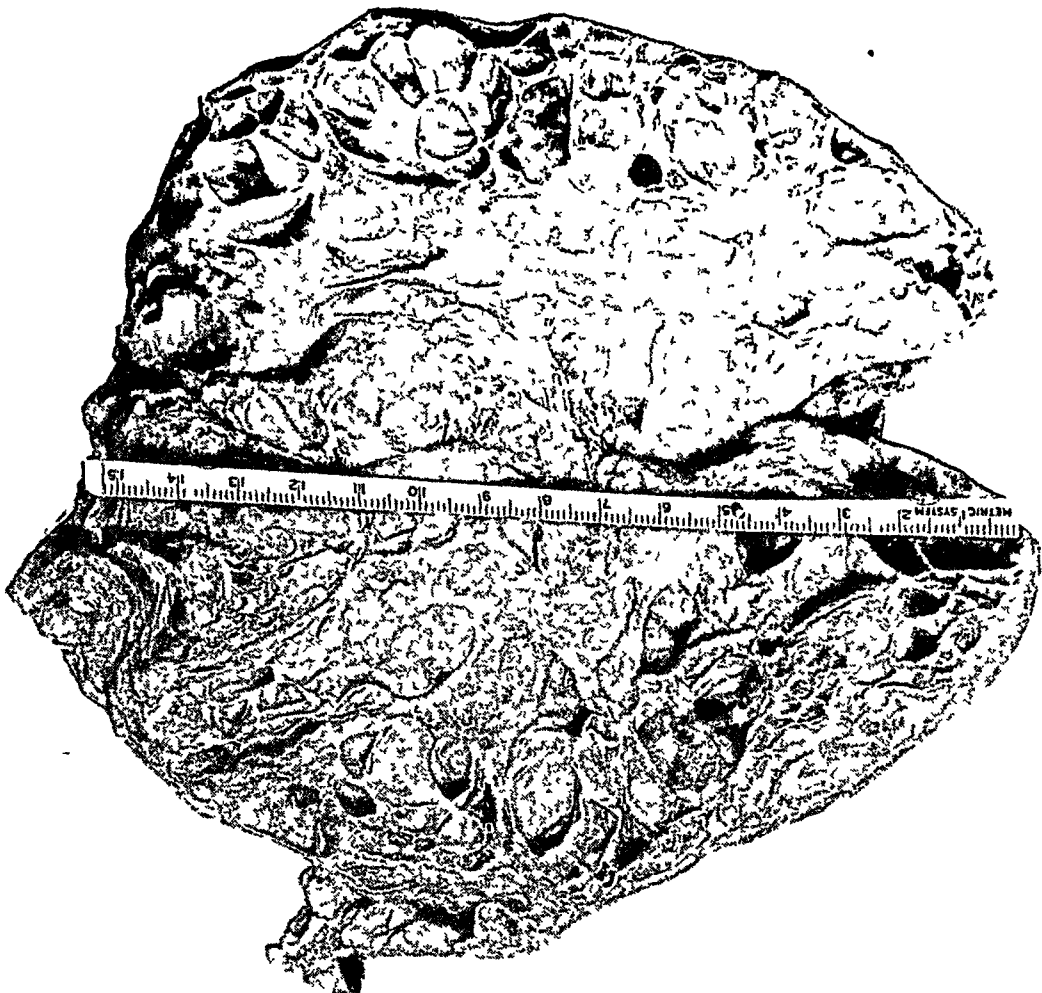


FIG 3 Case II Bilateral congenital polycystic kidneys, with multiple pea to walnut size thin walled cysts The cut surface of the right bisected kidney and the capsular surface of the left kidneys are shown

The second case presented the four cardinal manifestations of Addison's disease—asthenia, hypotension, pigmentation, and gastrointestinal disturbance, associated with marked dyspnea. Although the patient was sent to the hospital for transfusion, the anemia was not an important consideration. Because of the age of the patient, 59, the possibility that the masses in the flanks were congenital polycystic kidneys was considered only to be dismissed. Despite the fact that terminal renal insufficiency usually occurs during early adult life in individuals with polycystic kidneys, the marked degree of nitrogen retention in the blood, associated with the bilateral nodular masses, should have more strongly suggested polycystic kidneys. It is noteworthy that pigmentation was not given consideration prior to hospitalization. The existence of hypotension in the presence of such marked nitro-

gen retention in the blood is worthy of special comment.

#### SUMMARY AND CONCLUSIONS

1 Addison's syndrome includes four cardinal clinical signs: melanosis, asthenia, hypotension and gastro-intestinal disturbances. Occasionally, hypotension is not encountered until late in the course of the disease.

2 Tuberculosis of the adrenals is by far the most common autopsy finding in cases of Addison's disease. In the remaining cases, syphilitic adrenalitis or neoplastic invasion are most often responsible for the development of adrenal insufficiency.

3 In two cases reported herewith, Addison's syndrome was related to agenesis and hypoplasia of the adrenals in one case, and to pressure atrophy of the adrenals produced by congenital polycystic kidneys in the other case.

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# The History of Certain Medical Instruments

By LOGAN CLENDENING, M D,  
*Professor of Clinical Medicine, University of Kansas, Kansas City*

**G**ALILEO Galilei was attending a service at the Cathedral at Pisa (the date was circa 1581). He was not much interested in the sermon or the prayers, but his attention was directed to a chandelier which swung backwards and forwards above his head

The lack of interest Galileo displayed in the blessed mutter of the mass that day in the Cathedral of Pisa has worked entirely to our benefit. Galileo was the scion of a noble Tuscan family and had become a student in medicine at the University of Pisa, much to his father's disgust, because the paternal desire was to make a cloth merchant out of him. He was to live to plague both his father and the dignitaries of all Italy, first by dropping weights from the leaning bell tower at Pisa, (which made him look like a fool to his father), and then by inventing a telescope with which "his Serenity and all the members of the Senate" (of Venice) could, after having "ascended at various times the highest bell towers in Venice to spy out ships at sea making sail for the mouth of the harbour," see them clearly, though "without my telescope they

would have been invisible for more than two hours." His final outrage against public decency, of course, was to assert that the earth moved round the sun.

But all this was in the future. He was a medical student there in the Cathedral of Pisa when his roving eye lit upon that oscillating chandelier. It moved backwards and forwards like a pendulum in swings of ever decreasing amplitude. But what occurred to Galileo was that he thought he could calculate that even when the amplitude of the oscillation was the narrowest the time consumed in the small swing was the same as the time consumed in the long swing. This seemed queer; there was nothing like it in Aristotle; he was sure but was it true? Galileo had no watch. No one had a watch in those days. As he cast about for something to confirm his suspicions his fingers lit upon his pulse. Perhaps in the excitement of being on the verge of a discovery the young medical student felt his own heart beating and that suggested a timing piece.

At any rate, there he is—gazing upwards open mouthed, hand on wrist, while all about him the pious are crossing themselves and telling their beads.

Now! The chandelier swings—one—two—three—in three beats of his

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\*Read before the American College of Physicians, February 11, 1930, Minneapolis, Minn

pulse And back one—two—three Now several minutes later See the arc of the swing is much smaller now—you can see the corner of that window beyond its lefthanded excursion which you could not do before But as to timing—one—two—three, and back—one—two—three Just as before

Galileo Galilei walked out of the cathedral into the bright sunshine which was then as now beating upon those white marble stones, and he began to think He was by occupation a medical student so part of his thoughts concerned his pulse, this perfectly regular chronometer inside his body There was food for thought there But Galileo at the bottom of his soul was a mathematician And mathematics had to do with time and weight and length of arc—all the things which seemed so mysterious about that chandelier Heaven only knows how many people had seen chandeliers swinging in Cathedrals without ever having them suggest some relationship between those curious ponderables—time and weight We in this age live very much by time But the existence of time was less imminent in the days of Galileo It was only because his mind was that of a natural mathematical genius that he began to analyze these relationships Thus from Galileo's thoughts two ideas sprang—one concerning the timing of the pulse and one the relation of a pendulum's weight and arc to the period of its swing

He went home and began to experiment He tied a weight on a string and found that by exact measurements he had been right in the Cathedral

The pendulum swung through narrow arcs at the same rate of time that it did through wide ones But he found that if he lengthened the pendulum it swung through its arcs at a slower rate So much for the mathematicians

Then the medical student came to the fore He began comparing his own pulse under different conditions—after running and at rest—and found it varied Then the pulses of his friends—old people and young people There were variations here, too So he constructed the first instrument with which to measure the pulse—Galileo's Pulsilogium It was a very simple contrivance based on his string and weight idea The string wound up on a wheel behind a dial The dial had a pointer on it When the pendulum swung synchronously with the patient's pulse the pointer indicated the rate at which that pulse was going

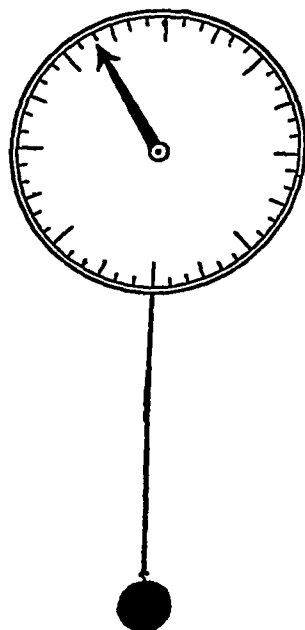


FIG 1 Galileo's Pulsilogium The pendulum was synchronized with the pulse and then the dial pointed to the rate of the pulse (From Harts' "Makers of Science," Oxford University Press)



It was long before this idea of Galileo's began to be used as a practical thing in medical diagnosis. The age was not ripe. It is true Galileo's great contemporary, Kepler, used his pulse to record astronomic observations. And when Galileo went to the University of Padua as professor of mathematics in 1592 he doubtless interested the professor of medicine there, Santorio Santorio, usually known as Sanctiorius. In 1625 Sanctorius published his comment on the first book of Avicenna and there describes a pulsilogium much like Galileo's.

Thus for the first time began the examination, and the counting of the pulse as an indication of the body's condition. It is today so fundamental and useful a procedure that it seems incredible it has been used for so short a time. Indeed, as we shall see, it is only within a hundred years that its significance became exact and valuable.

No wide use of the observation of the pulse as a method of diagnosis was made until the beginning of the eighteenth century. In 1707 a quaint little book called "The Physician's Pulse Watch" was published in England by a Staffordshire physician, Sir John Floyer.

Floyer says in the introduction to his book—"I have tried pulses by the minute in common watches and pendulum clocks and then used the sea minute glass."

We may imagine him starting to count a pulse and turning an hour glass upside down, counting the pulse until the sand had all run out. Science stumbles painfully along to its technical perfections.

"At last he was more happy. One Daniel Quare, a Quaker, had in the last years of the 17th century put on watches what Floyer called a middle finger, as we say a hand.

"Floyer's pulse watch ran 60 seconds and, you may like to know, can be had of Mr Samuel Watson in Long Acre."

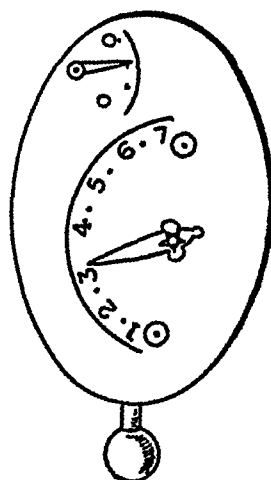


FIG 2 Floyer's Physician's pulse watch (From Dr S Wier Mitchell's Address—see Bibliography)

"And now follow pulses of age and youth, pregnancy, exercise and sleep. And we learn how diet, blisters and the weather affect the pulse."\*

For a time after Floyer's physician's watch was put on the market a vogue of wild speculation and theorizing about the pulse occurred. "If any man," says Dr Weir Mitchell, "wishes to nourish a taste for cynical criticism let him study honestly the books of the 18th century on the pulse. It is observation gone minutely mad—a whole Lilliput of symptoms—an exasperating waste of human intelligence. I know few more dreary deserts in medical literature from the essay on the 'Chi-

(\*Quoted from Mitchell—History of Instrumental Precision in Medicine)

nese Art of Feeling the Pulse," with which Floyer loaded his otherwise valuable essay, to Marquet's method of learning to know the pulse by musical notes, an art in which he was not alone. And error died hard. The doctrine of the specific pulse, a pulse for every malady, although rejected by de Haen, is in countless volumes, and survived up to 1827."

The next figure in the history of pulse counting is Robert Graves. You might see him often on the streets of Dublin a hundred years ago, a tall and distinguished figure, making his way to the Meath Hospital. Dublin was the great center of all European medicine for a period of several years at this time. And Graves was its most distinguished medical ornament. He had an interesting life behind him. While taking a walking tour in Austria, during his student days he was arrested as a German spy. He proclaimed his British citizenship, as one of his ardently patriotic Irish biographers insists, with unconscious humour, but nevertheless his captors threw him into gaol because they insisted no one could speak as good German as he spoke and still be an Englishman.

Among his many contributions to clinical medicine was the practice he introduced of counting the pulse by the watch. And he put it on a more scientific basis than Floyer had. He made regular records and watched the outcome of his patients so studied. It was Graves who established the science of pulse counting so that, as Weir Mitchell says, "the familiar figure of the doctor, watch in hand came to be commonplace."

### THE THERMOMETER

The exact measurement of heat also began, apparently, with Galileo, who also invented an air thermometer. It was a very delicate instrument, as it consisted of a glass tube of small bore

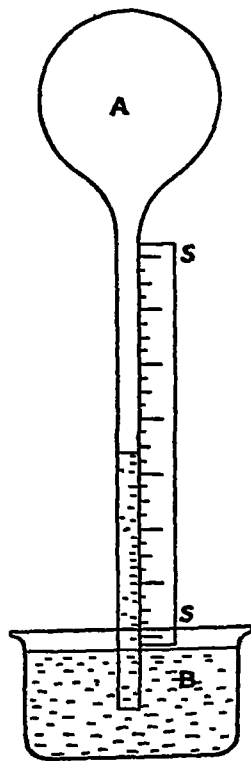
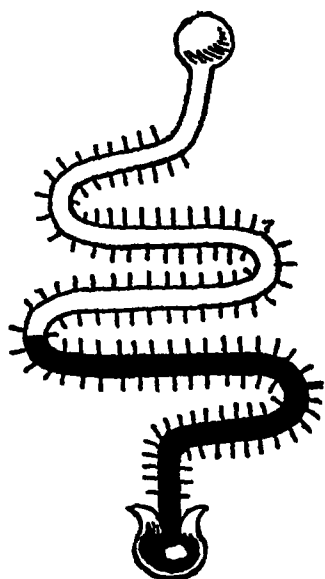


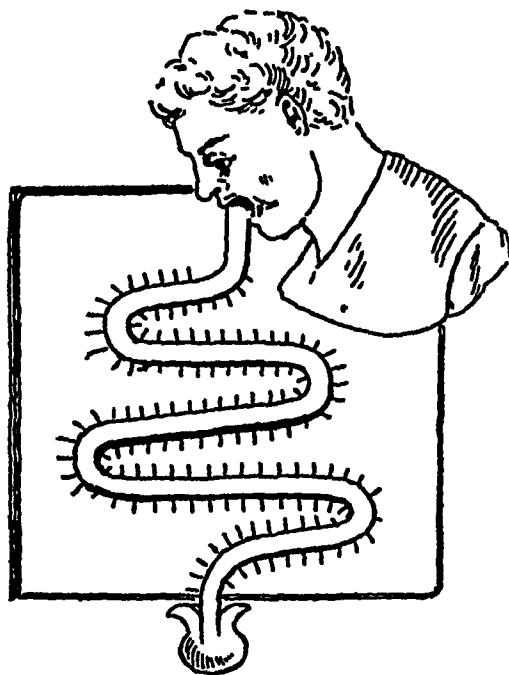
FIG 3 Galileo's air thermometer. The mechanism—as heat expanded the air in the bulb A the liquid was forced downward in the tube. From Harts' "Makers of Science," Oxford University Press.)

dipping into an open glass of colored liquid, it was subject to barometric fluctuations, and was totally impractical to carry around so as to measure body heat. Later closed thermometers were developed, also by Galileo. Santorius, the Paduan, also used thermometers, and left illustrations of their use.

When standards of measurement were proposed by Sir Isaac Newton and the familiar Fahrenheit, about



A The instrument



B The instrument in use

FIG 4 The first clinical thermometer modelled on the air thermometer of Galileo

It was invented by Sanctorius, and is

1701 and 1714 respectively, they fixed as natural points the freezing point of water and the temperature of the normal healthy body. There were many errors due to the inaccuracies of early observation. They are too complicated to go into here and not germane to our discussion. Fahrenheit took the freezing point of water as zero, and the temperature of the body as 100. As we know the latter had to be changed so that now on the Fahrenheit scale it stands at  $98 \frac{2}{5}$ .

The idea of the fluctuation of bodily temperature had been familiar since early times. But, of course, no exact record of the temperature of the body could be made until thermometers with a standard of measurement had been invented and generally introduced. The first work after Newton and Fahrenheit's establishment of a scale and the latter's invention of the mercury thermometer (which occurred about 1710) was done by a Scotchman, George

Martine. In his "Essays and Observations" (1740) he made an extended comparative study of the matter. And his friend and fellow Scot, James Currie, who threw water on ship deck over his men with fever, adds to every one of his reports (published in 1798) on the use of water in fever a record of the temperature.

Napoleon had his temperature recorded. Dr Archibald Arnott, Surgeon of the 20th Regiment, on April 21st, 1821, reported "as a result of the examination" of the Emperor's person he "could find no tension or hardness of the abdomen, the pulse was tranquil, the heat moderate." On April 3rd, "he passed a tolerably tranquil night, and slept a good deal, his pulse was 76, heat 96."

Certain ideas began to gain ground in the 19th Century. These were that in the normal body only the slightest variation of temperature occurred from time to time. Then there was

recognized a certain class of diseases—the fevers—which had an elevation of temperature. This knowledge was based on the recording of only one measurement of temperature—once in the course of the disease. Heart disease, dropsy, simple fractures, cancer, paralysis, dyspepsia were some of the diseases which did not have fever. Typhus, enteric, malaria, consumption, smallpox, hospital gangrene—some of the diseases which did have fever. Such was about the state of knowledge in 1850.

Around about 1850 a number of things began to occur. A young Manchester brewer read a paper at the British Association meeting at Oxford in 1847. The paper was on the subject of heat. The young man's name was Joule. His paper described how a falling weight made so much heat measured by having it fall on a baffle

plate in a vessel of water. The queer young man named Joule seemed to think that the higher the height from which the weight fell the more heat there was produced. In fact he had it all figured out. The standard was 778 foot-pounds of work, the mechanical equivalent of the pound-degree Fahrenheit.

Joule had been expounding these ideas in Manchester for some time. He gave popular lectures on them. Like most popular lectures no one attended them. He finally managed to get on the program of the British Association, but since his ideas were evidently so wild, since he was not a *research professor*, and since he had given popular lectures, the chairman whispered to him to make the paper as brief as possible. No one seems to remember who that chairman was.

"Discussion," said Joule himself, describing the incident, "not being invited, the communication would have passed without comment if another young man had not risen in the section and by his intelligent observations created a lively interest in the new theory. His name was William Thomson."<sup>†</sup>

Everybody up to that time had supposed heat was a substance—phlogiston. One of the great theorists of 18th Century medicine based his doc-



FIG 5 Statue of Joule in Manchester

<sup>†</sup>Nearly half a century afterwards when Lord Kelvin unveiled a statue to Joule in his native Manchester (a statue I am happy to say, which shows him in a bathrobe and slippers) he said—"I can never forget the British Association at Oxford in 1847 when I heard a paper read by a very unassuming young man who betrayed no consciousness in his manner that he had a great idea to unfold."

trine on this phlogiston theory But these new ideas indicated it was a form of motion—of energy. How could a weight falling gain heat? Young Mr Thomson, who discussed Joule's paper and who afterwards became Lord Kelvin, took the ideas of Joule and a forgotten Frenchman, Carnot, and established our modern ideas of the nature of heat and an absolute scale of heat and an absolute scale of temperature

Thus, as she has done over and over in her history, medicine gained from another science, physics, an important conception of the nature of bodily heat It was not to come to its fullest fruition for some time Its first fruit was clinical thermometry

The first application of this new knowledge of heat to sick people had to wait really a surprisingly long time for its development When it came it was from the new German school of medicine and it is coincident with the rise of that method of teaching which still retains its supremacy to our own day

The first great schools of medicine in Europe to which all students trooped were the Italian In the Renaissance period when anatomy was the new and fascinating subject the Universities of Padua, of Bologna and of Pavia were great centers of liberal thought In the later 17th and 18th Centuries the Italian universities divided honors with the schools of the Low Countries—Boerhaave was at Leyden, and Tulp at Amsterdam British medicine was plainly in the ascendency from 1780 to 1830 with the London, Edinburgh and Dublin schools vying with each other Then for a time the French under Laennec

and Broussais and Louis and Trouseau succeeded them so that it was just as fashionable for a young man to go to Paris after completing his studies at home as, for instance, did Oliver Wendell Holmes and James Jackson, Jr, as it is now for him to go to Vienna

But in 1840 there came to the chair of medicine at the University of Berlin a fat little boor named Schonlein Schonlein's methods of teaching revolutionized medicine because he made the patient the center of all discussion In other schools the teacher would enter the classroom, choose any subject he liked and treat the assembled students to an harangue on the subject more or less interesting or apt as the case might be But not so Schonlein He held his classes in the wards of the hospital He had his chair placed by the side of a particular patient Sinking into it he would hear the patient's story read then he would discuss that story with the students and in German, not in Latin. Then the professor would rise and examine the patient, by looking at eyes, ears, chest, abdomen and listening with the stethoscope again sinking back in his chair he would ask the students to confirm his examination Then the report on the analysis of the urine and other microscopical investigations would be read and discussed A diagnosis of the cause and nature of the disease from which the patient suffered would be made, and methods of treatment explained If the patient died, a post-mortem examination of the body was made in the presence of the class and errors in diagnosis, if any, pointed out

It was not long before this eminently practical method of teaching became famous. The universal introduction of the stethoscope and of percussion, of uinalysis, the perfection of the microscope, the rise of the science of chemistry—particularly the vanishing of scruples about the examination of the body after death—all made the intensive development of this method of clinical teaching particularly easy at this time.

But something else happened—a circumstance which has helped as much as anything to make clinical medicine in Germany continuously vivacious. There arose a group of brilliant men who adopted Schonlein's method and who became bitter and scornful rivals of each other. Happy is that medical school which has on its faculty three or more intensely vivid clinical teachers who hate one another and despise their rival's methods and views. Stimulating is the mental atmosphere of such an establishment.

After Schonlein's death he was succeeded at Berlin by two men, Frerichs and Traube, who were bitter enemies

and intellectual opponents. They stalked by each other in the wards of the hospital followed each by his group of students without speaking, nor were even the students of one group allowed to speak to those of the rival.

So far as all this serves our account of the development of the thermometer into medicine, it is evident that in such an atmosphere of intense desire to make an accurate diagnosis every kind of a method was tried. Among them the thermometer. Traube was among the first to introduce it, beginning to use it in his clinic about 1850.

But the thermometers of those early days were not such as ours. They were nearly a foot long and required five minutes to make a record.

Doctor Lauder Brunton says

"I had the appointment of house physician in the clinical wards of the Royal Infirmary at Edinburgh in 1866 to 1867.

"When I entered on my duties I found amongst other apparatus for use in the wards a case containing two clinical thermometers, one straight and the other somewhat bent. Each was

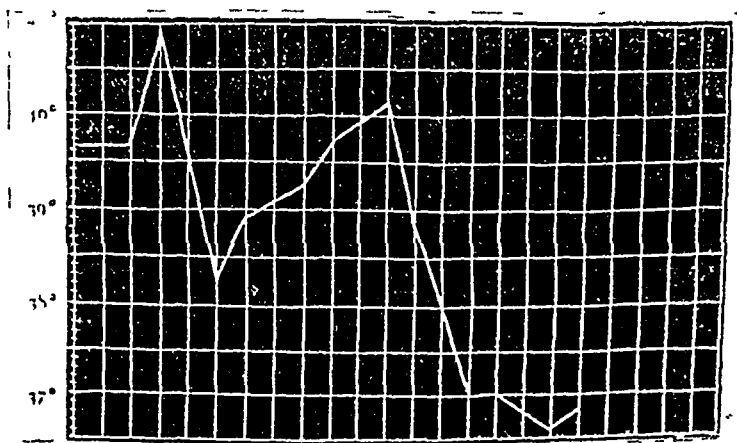


FIG 6 The first graphic record of temperature, which was made by Ludwig Traube (From Ebstein—see bibliography)

about ten inches or more in length and took about five minutes or more to reach the temperature of the body, when it was placed in the axilla. This thermometer case I used to carry under my arm as one might carry a gun."

Young Dr J S. Billings astonished his colleagues in the medical corps of the army of the Potomac by appearing on the field of battle with one of these gigantic temperature recorders. This was in 1862.

To illustrate the hardships of the early observers, Dr George H. Savage recalls that about 1866 he was house physician for Sir William Gull in London. Sir William Gull instructed him and another house physician to take the temperature of a group of typhus fever patients every hour. As they had to sit by the patient for five minutes and bend over the mouth to read the thermometer (the thermometers were not self-recording such as the ones we use now and can shake down) they spent most of their time in close proximity to typhus patients, and Dr Savage's associate came down with the disease himself.

These attempts were spasmodic and irregular. Only one record of a temperature in the course of any illness was generally taken—usually at the first visit.

But there was a hush of expectancy in the air of medicine about 1865 whenever the question of a patient's temperature was mentioned. Every wise clinician knew that there was something significant about it.

What was needed was some systematization of the procedure. It occurred to Dr. Carl August Wunder-

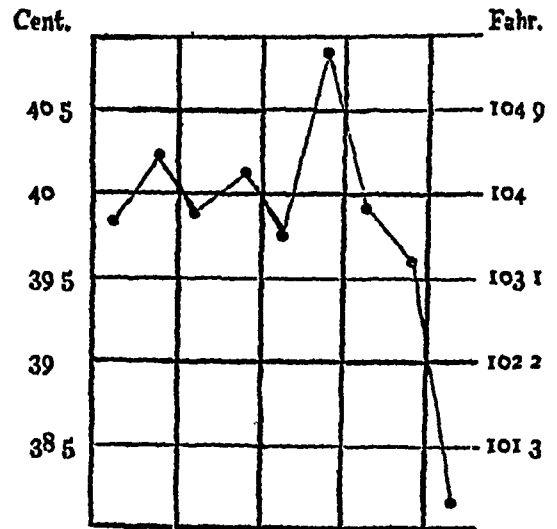


FIG 7 Graphic record of temperature in Wunderlich's "Das Verhalten der Eigenwärme in Krankheiten"

lich, who was professor of medicine at Leipzig, that possibly each febrile disease—each fever—had a characteristic *kind* of fever. He began to investigate. He laid down certain rules for himself. The thermometer must be convenient. It must record the temperature in a reasonably short time. It must be placed in some part of the body where it is entirely surrounded by body heat. The armpit, or axilla, was the favorite place selected by Wunderlich. But he also tried the mouth and the rectum.

Then in his large hospital he began to take temperatures every four hours on all patients. And before long he had plots and plans of temperatures which were just what he had suspected.

Here was a typhoid fever, for instance, carried along day after day—a slow rise in the beginning, a steady maintenance of fever for a week or ten days, then a slow daily drop—termination by lysis.

Here was pneumonia—entirely different—a rapid rise to dizzy heights—

a maintenance for seven or eight days—then a sudden drop—fall by crisis

Here was tuberculosis—still another form—a monotonous day after day recurrence of low temperature in the morning and high temperature in the evening

So, in 1868, Wunderlich published his results in a masterly book called in its English translation "Medical Thermometry" (*Das Verhalten der Eigenwärme in Krankheiten*). In its preface he gives all due credit to his predecessors—to George Martine and James Currie and Traube, as well as to all the workers in the pure science of physics, Galileo and William Thomson

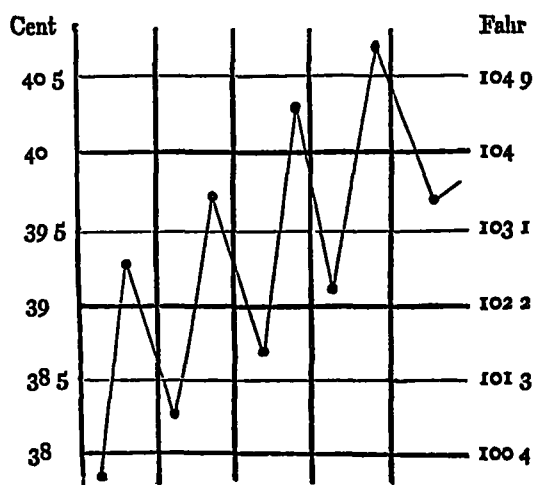


FIG 8 Graphic record of temperature in Wunderlich's "*Das Verhalten der Eigenwärme in Krankheiten*"

Technical improvement in the thermometer occurred, too. The large ones were replaced by small neat affairs, registering the index on an ivory plate below which the bulb protruded one inch

About the same time as the publication of Wunderlich's book Dr Clifford Allbutt invented and introduced

the small self-recording clinical thermometer much as we have it now

### THE SPHYGMOMANOMETER

The curate of Teddington in Middlesex from 1708 to 1761 must have been an interesting man. His name was Stephen Hales. He is one of the few clergymen one of whose sermons I should like to have heard. They were probably little filled with theological speculation, nor, I imagine, did the curate of Teddington, who was also rector of Porlock and of Faringdon, bother himself much with parochial duties. He would appear to have spent his life measuring the rise of sap in plants and the pressure of the blood stream in animals.

His ecclesiastical career is likely to puzzle an average American accustomed to seeing the vicars of God doing nothing but saving souls with great ardour unless one is familiar with "Barchester Towers." Here in the person of the Reverend Vesey Stanhope, who, though he had the livings of three cures, had resided for twelve years in Italy, you have the picture of the typical product of the Church of England system during at least most of the 18th and 19th Centuries. To this caste the Reverend Stephen Hales belonged. He was interested in Nature not in God.

He recorded his first observations on blood pressure in 1733, which he says, were performed about "twenty-five years since, that is when he was first presented with his incumbency. They were performed on the cural arteries of dogs. Afterwards he experimented on "two horses and a fal-



low Doe" His first experiment on hoises he records thus

"In December I caused a mare to be tied down alive on hei back, she was fouiteen hands high, and about fouiteen years of age, had a Fistula on her Withers, was neither very lean, nor yet lussy Having laid open the

left cruial Artery about three inches from her belly, I inserited into it a brass Pipe, whose bore was one-sixth of an inch in diameter, and to that, by means of another brass Pipe which was fitly adapted to it, I fixed a glass Tube of nearly the same diameter, which was nine feet in Length Then

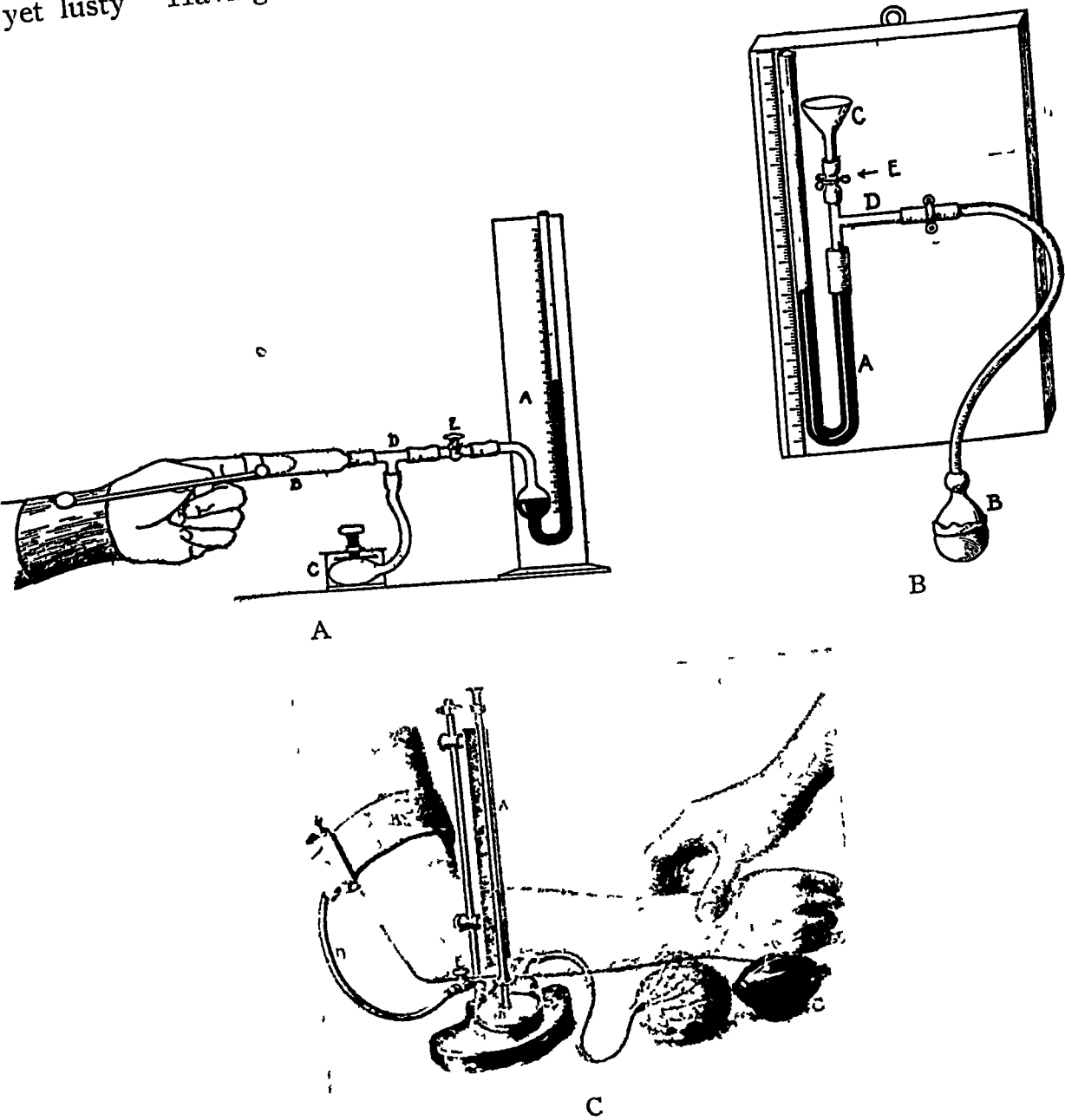


FIG 9 The evolution of the sphygmomanometer  
A Marceev's instrument—an early form  
B Von Basch's syhygmomanomter as modified by Zadek 1880  
C The Riva-Rocci apparatus—1896  
(All figures taken from Janeway's "The Clinical study of the blood pressure"  
Appelton & Co)

untying the Ligature on the artery, the blood rose in the Tube eight feet three inches perpendicular above the level of the left Ventricle of the Heart "

Following Hale's work the next advance in the study of blood pressure was the description of Jean—Leonard—Marie Poiseuille, in his graduating dissertation in medicine in 1828, of a hemodynamometer. This instrument measured the pressure by direct insertion of a cannula into the blood vessel, just as Hale's did, but it substituted a mercury column for the column of blood. Twenty years later, in 1847, Carl Ludwig added a float on the top of the mercury column and caused it to write on a recording cylinder, thus, as Stirling says, giving us at one coup "the kymograph or wave writer, and the application of the graphic method to physiology "

The first reading of the blood pressure in man was made in 1856 by Favre, who again used the direct method, connecting an artery with a mercury manometer in the course of an operation. He recorded the blood pressure in the femoral artery as 120 mm of mercury, and in the brachial artery between 115 and 120 mm. Albert in patients undergoing amputations, made similar observations.

The idea of indirect measurement of blood pressure seems to have originated with Karl Vierordt, professor of physiology at Tübingen, in 1855. Marey applied this method to clinical medicine. The apparatus he used was based on the principle of the obliteration of the pulse but was cumbersome inasmuch as the arm had to be placed in a glass box filled with water.

this was connected both with an instrument to record the arterial pulsation and a mercury manometer to record the pressure within the glass box. Von Bosch, using the idea of indirect measurement, greatly improved the instrument by using a ball filled with water and connected with a manometer to obliterate the arterial pulse. This was still further improved by Potain, of whose portable sphygmomanometer Vaquez says—"for an entire medical generation it was as useful in research as the clinical thermometer "

Potain, von Bosch, Zadek and others made during this period the first regular measurements of the arterial blood pressure in man. They found it to be 130 mm of mercury, but with variations between 110 and 160 mm. They noted measurements in patients with arteriosclerosis as high as 180 to 200 mm of mercury and in fever patients 90 or 100 mm. These familiar figures, never improved upon or needing revision, show that the instrument was accurate and the observers painstaking.

In 1896 Riva-Rocci demonstrated an apparatus before the Italian Congress of Medicine which serves as the model for all of our present instruments. It consisted of a rubber bag or cuff which encircled the arm and was protected by an inelastic covering. This rubber bag was capable of having its internal pressure increased, and was connected with a mercury manometer. In 1897 Hill and Barnard substituted a calibrated pressure gauge for the mercury manometer. Every modern instrument for the reading of blood pressure clinically has followed the plans of these innovators.

## THE HYPODERMIC SYRINGE

I cannot conclude this review without mentioning an instrument of therapeutic value. The history of the origin of hypodermic medication is confused. Garrison gives credit to Francis Rynd of Dublin for having "first employed hypodermic injections by a gravity device (of his own invention) for the relief of pain (1845-1861)." But

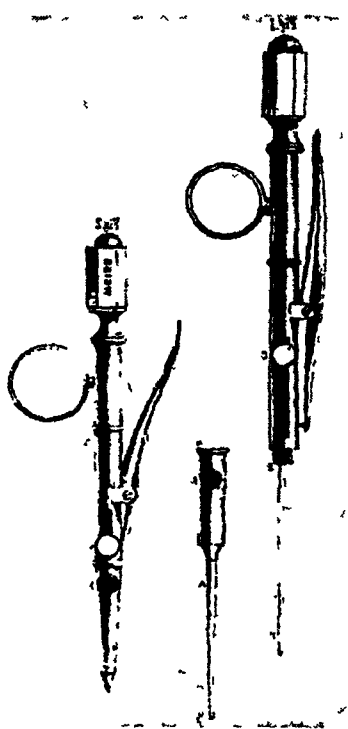


FIG 10 Rynd's Hypodermic Syringe (Photograph of the plate in the Dublin Quarterly Journal of Medical Science, 1861 XXXII, 13)

Singer says—"No advance of this order compares in importance with the introduction of the Hypodermic Syringe by the ingenious French surgeon Charles Gabriel Pravaz (1791-1853)."

In 1836, however, another French physician, Lafargue, used a sort of needle trocar for introducing morphine under the skin in paste form. Previously an incision was made in the skin and the morphine placed in the wound.

It is said that Doctors Taylor and Washington of New York in 1836 introduced morphine under the skin with a syringe of sterling silver with a leather piston but an incision had to be made in the skin to allow the nozzle to be inserted. A cutting point on the needle was introduced by Dr Charles Hunter of London in 1859.

What Pravaz did was to use a separate needle with a slip joint. In many French hospitals hypodermic needles are known as Pravaz. Apparently the first all glass syringes began to be made by Luer in 1896. Rynd's description of his syringe is as follows:

"The cannula (a) screws on the instrument at (b), and when the button (c), which is connected with the needle (f), and acted on by a spring, is pushed up (as in Fig 2), the small catch (d) retains it in place. The point of the needle then projects a little beyond the cannula (Fig 2). The fluid to be applied is now to be introduced into the cannula through the hole (e), either from a common writing-pen or the spoon-shaped extremity of a silver director, a small puncture through the skin is to be made with a lancet, or the point of the instrument itself is to be pressed through the skin, and on to the depth required, light pressure now made on the handle raises the catch (d), the needle is released, and springs backwards, leaving the cannula empty, and allowing the fluid to descend. If the instrument be slowly withdrawn, the parts it passes through, as well as the point to which it has been directed, receive the contained fluid and still more may be introduced, if deemed expedient."

"The subcutaneous introduction of fluids, for the relief of neuralgia, was first practiced in this country by me, in the Meath Hospital, in the month of May, 1844. The cases were published in the 'Dublin Medical Press' of March 12, 1845. Since then, I have treated very many cases, and used many kinds of fluids and solutions, with variable success. The fluid I have found most beneficial is a solution of morphia in creasote, ten grains of the former to one drachm of the latter, six drops of this solution contain one grain of morphia, and a grain or two, or more, may be introduced in cases of sciatica at one operation, with the very best

effects, particularly if they are of long standing, or even in cases of tic in the head and face, with equally beneficial results. The small instrument is for operations on superficial nerves, the larger one for deep-seated nerves, for though it is not necessary to introduce the fluid to the nerve itself to ease pain, still the nearer to the seat of pain it is conveyed, the more surely relief is given. They were manufactured, and completed entirely to my satisfaction, by the celebrated surgical instrument-maker, Mr Weiss, of London, and are faithfully represented in the accompanying lithograph, by Foster & Co, of this city."

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## Editorials

### *THE BACILLUS-CALMETTE-GUERIN TRAGEDY IN LUBECK*

On the 27th day of July, 1929, Calmette sent a culture of the BCG-strain, Number 734, to Obermedizinalrat Dr Altstaedt, Director of the Lubeck Gesundheitamt. With this same culture 573 children had been inoculated in France without apparent harm, and parallel cultures had been sent to Mexico and Riga and nothing unfavorable heard from them. In Lubeck the preparations for organization for a campaign in favor of inoculation with this culture, in the way of propaganda, lectures to physicians, instruction of midwives, etc., extended to February, 1930. In the meantime the culture was kept in the laboratory of Prof Deycke in the Allgemeines Krankenhaus in Lubeck, and grown, at first, upon bile-potato medium, then later upon the Hohn egg-medium, in part upon hematin-egg medium, and at the last only upon the egg-medium. Transfers were made every four weeks by an experienced laboratory helper who had been with Deycke 17 years. The medium recommended by Calmette (synthetic fluid of Sauton) was not used. For the growth of the cultures and the preparation of the material for inoculation no completely separate compartment was used. No virulent human tubercle-bacilli were present in the incubators until September, 1929, the earlier cultures present

having been killed by over-heating to 80° C. In September Deycke obtained a virulent strain of human tubercle bacilli, which was placed in the same compartment with the BCG inoculation preparations, and partigen was prepared according to the method of Deycke-Much, while the BCG cultures were kept exclusively in a smaller compartment of the incubator. As to the possibility of any mistake in the cultures, the BCG cultures were grown exclusively on *solid* media, the virulent strain on *fluid* media. On the day before the inoculation the material was tested for acid-fast organisms and found to be free from them. The inoculations were carried out in the children through the midwives exactly according to the French method, and the whole organization met the requirements of the French model. A dose (10 mg) of the culture material as prepared for inoculation was given by mouth three times. About 50 per cent of all children born during the critical 60 days were inoculated, the total number of inoculated being 245. On the 17th of April, 1930, the first child died 33 days after the first inoculation. No autopsy was made. On the 20th of April, 54 days after the first inoculation the second child died. The autopsy showed a marked tuberculous process in the lungs, moderate organs. This case was regarded as an acrogenous infection, since the

mother of the child had tuberculosis but which was apparently not an open one. On April 25 and 26 autopsies made on the third and fourth children dying, who had been inoculated, left no further doubt that the deaths had been caused by a true feeding tuberculosis. Of 74 children inoculated before the 25th of March, 17 died, and a careful examination of 41 living showed evidence of tuberculosis in 28. The last death occurred on March 25. Inasmuch as there were 130 children inoculated later, up to April 26, further cases and deaths are to be expected. The clinical symptoms of the inoculated infected cases were striking weakness and drowsiness after the inoculation, failure to gain in weight, meteorism, diarrhea, swelling of the cervical glands, and increase of temperature. In the more severe cases there was enlargement of the spleen, with roentgenologic changes demonstrable in the lungs. Some of the cases showed a characteristic cutaneous eruption, resembling pemphigus, which appeared after the second or third inoculation. The period of incubation in the 17 dead children was 4 weeks in 12 cases, 5 weeks in 3 cases and 3 weeks in 2 cases. On May 23, the incubation period in 47 still living children was estimated 3 weeks in 2 cases, 4 weeks in 10 cases, 5 weeks in 18 cases, 6 weeks in 11 cases and 7 weeks in 3 cases. In general, it was concluded that the prognosis was the more favorable, the longer the incubation period, but several children with a short incubation period ran a favorable course. The autopsy findings showed tubercles of varying size in all organs. A basal tuberculous

meningitis was not present in any of the cases, although in one case a single tubercle was found in the leptomeninges. A most profound impression was made by these tragic events upon those in Lubeck directly connected with the immunizing attempt. In the height of his excitement Deycke on the 26th of April destroyed all that remained of the inoculation material in his laboratory. This on the face of it would seem to have been a most unwise act, as it prevented further study of the material used for inoculation. It may be accepted without doubt that the culture originally sent by Calmette was in truth avirulent, this would seem to be proved beyond all doubt by the harmlessness of its use in France and elsewhere. There are but two possible explanations of the Lubeck tragedy. Either there occurred in Lubeck *in vitro* a reversion of the culture to the virulent form, or the Calmette culture was either exchanged for or contaminated with virulent tubercle bacilli. It is not possible at this time to say positively which of the two alternatives is the true explanation. Against the first hypothesis may be urged the fact that up to the present moment it has been impossible to convert the avirulent Calmette culture into a virulent one. Numerous animal experiments have been carried out in this direction with guinea-pigs inoculated with the Calmette bacillus, in the attempt to lower the resistance of the inoculated animals by injury to the animal, mixed infection, addition of toxin, avitaminosis, chilling etc. All of this experimental work failed to produce any increase of virulence in the Calmette organism. Further, in all of

the immunizing work that has been carried out upon animals with the Calmette cultures there has been no previous evidence of injury to any animal as the result of the inoculations. On the contrary, this experimental work has had favorable results in raising the resistance of the animals inoculated. For more than twenty years Calmette has busied himself with the problem of immunization against tuberculosis. On January 8, 1908, he for the first time began to cultivate a highly virulent form of bovine tubercle bacilli upon bile-potato medium, which after twelve years of cultivation upon bile-containing potato medium appeared to have completely lost its virulence. As the avirulence of this strain seemed to be fully established in 1921 he began most carefully to test it in children. In correspondence with his view that spontaneous tuberculosis infections arise through the gastro-intestinal tract he gave the prepared cultures in doses of 10 mg, three times, per os, to newborn children, before any possibility of infection from the environment could take place. In children exposed to virulent tubercle bacilli he found an apparent protection from infection. The number of infants inoculated with the BCG cultures must now reach 300,000-400,000. Of these over 242,000 were in France. With the experience of such a material, any harmful

effect of the inoculation, any virulence of the culture, or an acquired virulence in the bodies of the inoculated children would certainly seem to be wholly excluded. Even if such occurred in only a relatively small per cent of the inoculated, the number of such would reach 4000 or more cases, and such a number of unfavorable results could not be kept concealed. In truth, no such harmful effects have ever been observed. It can readily be seen, therefore, what a catastrophe the tragic events in Lübeck must be to Calmette and his adherents. Naturally a storm of discussion has been aroused by the sad occurrence, especially in Germany where physicians were very slow to take up the Calmette work. Indeed, the direct stimulus to the Lübeck experiment was a personal letter from Calmette, accompanied by a culture of the BCG strain, written in July, 1929. In fact, a certain reproach against Germany's slowness to accept the Calmette work, had already been heard in other countries that had begun immunization work. It is but natural that the uncertainty as to the cause of the Lübeck fatalities should lead to a marked set-back to the Calmette work, but, as expressed by Professor Lange of the Reichsgesundheitsamt, the disastrous results at Lübeck offer no sufficient grounds for an unfavorable judgment of the BCG method of immunization.

## Abstracts

*The Hormone of the Adrenal Cortex* By FRANK A. HARTMAN and KATHERINE A. BROWNELL (Proc of the Soc of Exper Biol and Med, June, 1930, p 938)

These authors have previously demonstrated that an extract which will definitely prolong the lives and ameliorate the symptoms of adrenalectomized cats can be made from adrenal cortex. They have proposed the name of cortin for this hormone, which is essential to life. Heat (80° C for 5 minutes) destroys it. It is lost upon repeated precipitation with NaCl. Therefore some other method of concentration must be employed. An extract of any desired concentration can be obtained by extracting the cortex with ethyl ether. After removing the ether *in vacuo* the residue is extracted with warm 80% alcohol. Chilling precipitates much inactive material. Removal of the alcohol *in vacuo* is followed by the extraction of the residue with water to make the desired concentration, or extraction by alcohol is repeated for further purification. Completely adrenalectomized cats treated with this extract not only live indefinitely in good condition, but are also able to meet unusual demands as well as normal animals. They can undergo major operations, and the wounds heal promptly. They seem to resist infections to which untreated adrenalectomized cats often succumb. One cat had an abortion following the removal of the second adrenal, and bled for several days afterward. Yet by the use of this extract she recovered. Another cat was etherized and thoroughly explored for accessory adrenals 136 days after the removal of the second adrenal, with recovery as prompt as would be expected in a normal cat. If adrenalectomized cats are given more extract than is necessary to keep them in fair condition they eat more and gain in weight. Blood urea remains within the normal range. One adrenalectomized cat

has been rescued from the final stage of prostration due to an inadequate supply of cortin 3 times by injection of extract. The last time dyspnea and convulsive twitchings had developed. Seventy minutes after the injection of the extract the cat was sitting up. In 85 minutes she was shivering. In 100 minutes she was eating, not merely tasting, but taking her usual quantity of food. Individual animals show great differences in the amount of cortin which they require as well as the frequency of injection needed.

*Some Metabolic Changes Occurring in Prolonged Diathermy Treatments* By E. S. NASSER and S. L. WARREN (Proc of the Soc of Exper Biol and Med, June, 1930, p 943)

Studies on the respiratory exchange and the sugar, non-protein nitrogen, chlorides and carbon dioxide content of blood, were made on anesthetized (morphine + amytal) dogs. Tracheotomy was done and connection made to a Benedict universal apparatus. Blood analyses were done by standard methods. The high frequency current had the following characteristics: wave length — 200 meters, relatively high voltage, currents from 500 to 1000 milliamperes. Electrodes were placed on the left upper arm and right thigh, or on either side of the head. Treatment continued from 1 to 3 hours. Temporary measurements were made with thermocouples and mercury wavometers. The respiratory metabolism invariably increased, in some cases 150 per cent. Body temperatures were elevated 5 to 7° C. When blood sugar was initially relatively high there was a gradual depletion during diathermy; in cases of low initial concentrations a preliminary rise was noted followed by a fall. The end result was a marked hypoglycemia (30 to 50 mg per 100 cc blood). Non-protein nitrogen was in some cases increased to 200 per cent.



of normal Chlorides failed to exhibit any gross changes. The carbon dioxide content of whole blood and plasma invariably dropped to a rather low level (about 35 vol per cent). Panting was induced in some animals, during which time the respiratory rate exceeded 250 per minute.

*Experimental Polyneuritis in Chickens Given Jamaica Ginger* By J H WATKINS (Proc of the Soc f Exper Biol and Med, June, 1930, p 900)

Four apparently healthy chickens weighing approximately one kilo each were used in this experiment. Jamaica ginger obtained from a community where there were many patients with peripheral neuritis was used. Two of the chickens received daily doses of 2 cc fluid extract of ginger and the other 2 received an equal amount of 83 per cent ethyl alcohol. The chickens were kept in a cage out of doors and given a diet of cracked corn and oats. Thirty-eight days after receiving the first dose of ginger and after each chicken had been given a total of 70 cc there was no signs of muscular weakness. There had been some loss of weight during this time. On the 39th day the two chickens receiving ginger showed slight motor weakness and loss of coordinating power in both extremities. Feeding ginger was discontinued at this time. During the next two days there was a progressive motor weakness and the difficulty in walking or standing was marked. Control of the feet was wholly lost, and the toes were turned under the feet when an attempt was made to walk. The legs rather than the feet were used to support the body when resting. There was apparently no sensory disturbance of the extremities and no edema was observed. A thick suspension of rice polishings was given through a tube when the paralysis was first observed and daily thereafter for a period of 5 days without any improvement. One of the chickens died 8 days after the onset without any improvement. This investigation is being continued with a larger number of chickens, employing ginger with phenol, ginger without phenol and ethyl alcohol. At the 9th day after the experiment was begun only those receiving phenol ginger showed any leg weakness.

*Effect of Sodium Salicylate on Intradermal Reactions of Rabbits* By O E HAGEBUSH and R A KINSELLA (Proc of Soc f Exper Biol and Med, June, 1930, p 922)

Sodium salicylate is commonly used in the treatment of infections, especially those presumed to be due to invasion by streptococcus. The old idea that acute rheumatic fever is due to infection by streptococcus, and the recently developed conception that the disease is involved in a process of allergy to streptococcus, stimulated this study of sodium salicylate in relation to allergy to streptococcus. Rabbits, inoculated with cultures of a strain of *S hemolyticus* of low virulence, were used for this study. Following the intra-cuticular injection of streptococci, purulent arthritis invariably resulted and persisted until the death of the animal. In the first series of animals 15 controls gave strongly positive intradermal reactions 10 days after the production of arthritis, and 8 animals, given sodium salicylate 24 hours before the production of arthritis and at 24 hour intervals thereafter showed slight or no intradermal response. In another experiment, 16 control animals gave strongly positive reactions, 28 animals receiving sodium salicylate, gave slight or no reactions. 4 animals receiving glycine alone gave strongly positive reactions, and 16 animals receiving mixture of glycine and sodium salicylate gave strongly positive reactions. From this work it seems possible to draw the following conclusions: Sodium salicylate suppresses the allergic dermal reactions of rabbits to filtrates of hemolytic streptococcus. This effect is most definite when sodium salicylate is given before the focus of infection has developed. There is no relation between the presence or absence of this dermal reactivity and the character of the vascular pathology.

*Primary Carcinoma of the Lung* By PAUL D ROSAHL (Amer Jour of the Med Sc, June, 1930 p 800)

The postmortem incidence of primary carcinoma of the lung is steadily increasing, and this increase is real and absolute. Combined statistics show that primary carcinoma of the lung at autopsy from 1910

to 1919 comprised 0.44 per cent of autopsies, and 4.39 per cent of all cancers. Since 1920, primary carcinoma of the lung comprised 0.89 per cent of autopsies and 6.98 per cent of all cancers. Primary cancer of the lung is not as rare as was formerly believed. Because of its increased frequency, the clinician should give this affection serious consideration in differential diagnosis in patients of the carcinomatous age presenting puzzling lung symptoms and signs. An early diagnosis will permit accurate prognosis, and in selected cases, perhaps, surgical therapy.

*Observations on the Possibility of Methyl Chloride Poisoning by Ingestion with Food and Water.* By W. P. YANT (Public Health Reports, May 9, 1930)

The danger of life from the escape of noxious or inflammable refrigerating media into the air is being given considerable attention in the design and installation of mechanical refrigeration devices. In addition to atmospheric contamination and possible poisoning by inhalation, however, attention must also be given to possible contamination of food and poisoning by ingestion. In the present popular design of these devices the cooling mechanism is situated inside the comparatively air-tight cabinet with the food, and small leaks, which might be insignificant from the viewpoint of appreciable contamination of the external atmosphere, would create high internal concentrations. While there is no definite evidence that food poisoning has occurred or that this type of hazard exists with the refrigerants in current use, nevertheless, the possibility is a matter of concern to manufacturers of refrigerating devices and products, to health officials and to the public. The Bureau of Mines, with the cooperation of manufacturers of methyl chloride ( $\text{CH}_3\text{Cl}$ ) has been engaged in the study of acute and chronic poisoning resulting from exposure to contaminated air. This work has been extended to include poisoning by ingestion. The possibility of poisoning by ingestion of methyl-chloride contaminated food and water was studied by exposing dogs. No apparent signs of poisoning were caused by the average daily

ingestion on four successive days of 550 grams of ground raw beef or 200 cc of milk that had been exposed 15 to 75 hours to 100 per cent methyl-chloride vapor at  $35^\circ\text{F}$ . No apparent symptoms of poisoning or changes in the hemoglobin and blood cells were caused by the ingestion of methyl-chloride contaminated water on 115 days of a total period of 171 test days. Also, no formates were found in the urine. Autopsy and examination of frozen sections, however, revealed a moderate degree of intracellular fatty degenerative infiltration affecting the ascending, descending and collecting tubules of the kidney. The glomeruli and convoluted tubules were apparently undamaged. Analysis showed the water to be 75 to 100 per cent saturated with an average methyl-chloride content of 0.595 gram per 100 cc of water. This was the only water given the animals on six days of each week of the test. The taste of water saturated with methyl chloride at  $68^\circ\text{F}$  is sharp, sweetish, and sickening when first taken into the mouth, followed almost immediately by a burning sensation. Persons would not drink more than a mouthful or two. It was frequently refused by the animals, even though they were deprived of other water.

*Ursache und Bedeutung der post-operativen Acidose.* By E. RAAB and F. WITTENBECK (Klin. Wochenschr., February 9, 1930, II 255)

After narcosis and operations variations in the acid-base balance take place. Since Criele in 1917 called attention to these changes they have been generally spoken of as a postoperative acidosis, when a lowering of the alkali reserve and increase in the hydrogen-ion concentration of the blood occur. In surgery the postoperative acidosis has received especial attention from many sides, and it has been generally regarded as a dangerous complication in the course of healing. Above all the American school has held the postoperative acidosis to be dangerous. This conception rests in part upon the fact that Reimann and Bloom found in numerous investigations a marked increase in ketone bodies in the blood. Their value often rises after operation to 225 mg. This

increase in ketone bodies has been generally held responsible for the lowering of the normal blood reaction. Further, a postoperative rise in the blood-sugar has been observed by other workers, and both phenomena have been regarded as related, namely, an increase in the blood-sugar goes hand in hand with an increase in the H-ion concentration. These postoperative phenomena affect the nitrogen metabolism, as has been demonstrated. For the neutralization of the acidosis the bicarbonate of the blood and the free ammonia given up from the liver was utilized. In the urine there occurs an increase in the ammonia value. Since these phenomena have never been completely studied in one and the same patient, but their study has been confined to scattered observations in one or the other metabolic directions, and in part studied on animals, and because of various contradictions, the authors undertook in their operations to study the cause and degree of the metabolic disturbances after operation and narcosis in human subjects. This was done in the case of nearly 100 patients. The hydrogen-ion concentration and alkali reserve were studied according to the methods of Hasselbach, Straub and Meier, the blood-sugar according to Hagedorn-Jensen, acetone and Beta-oxybutyric acid according to Engfeldt, ammonia according to Folin. As a result of their study the authors conclude that a number of factors are responsible for the postoperative disturbances of metabolism. A postoperative acidosis can sometimes arise through damage to the liver from inhalation narcosis. Disturbances of the hepatic function leads to pathologic products of metabolism, and to an increase of the acidity of the blood. The operation shock alone can, through the stimulation of the splanchnic, produce the same metabolic disturbances. Further, the psychical alteration of the patient before

the operation is of significance in the postoperative metabolic changes. The effects of the psychical excitation may be manifest before the operation. Further, the over-acidity of the organism through carbonic acid must be taken into consideration, due to the lowered excitability of the respiratory center through the anesthetic. When the paralysis of the respiratory center through the narcosis ceases, the acids of the blood again exert their full effect upon the respiratory center. This leads to an over-ventilation and to an increased output of carbonic acid through the lungs. So in many cases there will result an alkalosis of the blood although ketone bodies are present in the blood in increased amount. Finally, the hunger-state associated with the operation with its acidosis can increase the postoperative disturbances of metabolism. The administration of sodium bicarbonate can produce a normal blood reaction, but it has no influence on the cause of the metabolic disturbance. It should be emphasized that an alkalosis may be present after the operation. It follows that the methods of combatting the postoperative acidosis are useless, and may be even harmful. The authors insist that it is not necessary to treat the postoperative acidosis. In 100 patients they have never seen any damage to the organism due to the metabolic disturbances mentioned above. The body is always in a position to compensate for the postoperative disturbances of metabolism. They conclude with the statement that *the postoperative acidosis has no significance, and has no unfavorable influence upon the postoperative course. To avoid more marked metabolic disturbances after the operation the patient should have the least possible preparation for the operation. If any disturbance in the postoperative state occurs its cause is never to be sought for in postoperative acidosis*

## Reviews

*Varicose Veins* By H O MCPHEETERS, M D, F A C S, Director of the Varicose Vein and Ulcer Clinic, Minneapolis General Hospital, Attending Physician New Asbury, Fairview and Northwestern Hospitals, Minneapolis, Minn 233 pages, illustrated with half-tone and line engravings Second revised and enlarged edition F A Davis Company, Philadelphia, Pa Price in cloth, \$3 50 net

The frequency of varicose veins and ulcers and the unsatisfactory nature of the treatment usually accorded them are undoubtedly responsible for the interest excited by McPheeters book, the second printing of which was exhausted in less than five months A new edition has now been prepared to meet the demands created by this interest In it an attempt has been made to make more clear certain points that were not sufficiently understandable by the general practitioner Particularly in the case of the Trendelenburg test, both as to its demonstration and clinical application have so many inquiries been made that it has seemed best to present it in a separate chapter The general technic is practically unchanged, although slight modifications developed with greater experience have been made in it The work on the pathological changes following the injections has been continued by the study of biopsies made at intervals of one hour to two years following the injection The author states his views clearly and concisely

*Physiology and Biochemistry in Modern Medicine* By J J R MACLEOD, M B, LL D, D Sc, F R S, Regius Professor of Physiology in the University of Aberdeen, Scotland, Formerly Professor of Physiology in the University of Toronto, Canada, and in the Western Reserve University, Cleveland, Ohio Assisted by R G Pearce, A C Redfield, N B Taylor, and J M D Olmsted, and by others

Sixth Edition 1074 pages, 295 illustrations, including 9 plates in color The C V Mosby Company, St Louis, Missouri, 1930 Price in cloth, \$11 00

During the three years since the appearance of the last edition there have been no important discoveries in the field of physiology and biochemistry There has been, however, a steady increase in general knowledge This has been recognized, in the preparation of the present edition, in various changes and additions that have been spread throughout the volume Material that is out of date or no longer considered necessary has been omitted New matter has been put in its place, or has been placed in small print The size of the book therefore, remains unchanged It remains one of the best textbooks on physiology that has yet been written, and gives a very complete survey of the science of physiology as it stands today This book is heartily recommended to medical students

*Trauma, Disease, Compensation A Handbook of Their Medicolegal Relations* By A J FRASER, M D, Chief Medical Officer, Workmen's Compensation Board, Winnipeg 524 pages F A Davis Company, Philadelphia, 1930 Price in cloth, \$6 50

The increasing importance of workmen's compensation makes this volume of interest to medical men in Canada and America, inasmuch as the number of industrial casualties in these two countries reaches enormous figures, even greater than the casualties of the War Out of the large number of injured workers grow many problems which almost daily meet the medical and surgical practitioner, and are finally decided by Compensation Boards, which in the reviewer's experience, are all too often ignorant and incompetent Before such Boards opinions based upon scientific knowledge are often set aside by the judgment of an ignorant

and prejudiced Commissioner. If there is anything in the United States needing a thorough renovation from the bottom up it is our methods of taking testimony in Compensation cases, and in settling such claims. The workman and his relatives are usually favored in the grossest way, and the opinions of ignorant and inexperienced physicians are credited over those of scientific men of repute. The present volume has been prepared in the hope that a useful purpose will be served by assembling the opinions of representatives teachers and writers in the medical field on the difficult subject of the influence of trauma in giving rise to subsequent conditions of disease. Such information as exists upon this subject is scattered through the literature, and the statements made on this point are usually vague and casual. The opinions quoted are in the main verbatim. Every care has been taken not to distort the meaning of the writer quoted. The compilations of reputable and expert opinion on the question at issue will, it is felt, furnish a useful encyclopedia on a subject not heretofore covered in a general and comprehensive manner, and should aid medical men and industrial boards in arriving at an adjustment of debatable medical problems in this field. No claim is made for original work in the preparation of this volume. The work has been largely that of an editor in assembling and arranging the material selected, and the author assumes no responsibility for the opinions set forth. If medicolegal testimony in the field of industrial compensation is to be put on a decent basis in this country, reference book of authority will constitute the foundation for such, and this volume is a step towards the securing of that foundation. It is however, very superficially done, and the range of literature covered by it is very limited. It is a pity that the editor-author could not have had access to the extensive German literature on the subject.

*The Normal Diet. A Simple Statement of the Fundamental Principles of Diet for the Mutual Use of Physicians and Patients.* By W. D. SASSER, M.S., M.D., F.A.C.P., Director of the Potter Metabolic Clinic, Department of Metabolism,

Santa Barbara Cottage Hospital, Santa Barbara, California. Third Revised Edition. 134 pages. The C. V. Mosby Company, St. Louis, Mo., 1930. Price in cloth, \$1.50.

The author has for many years given the subject matter of this book in lecture form to patients suffering from various nutritional disorders. He believes that errors in diet are very common, and that such errors are responsible for many minor ailments as well as some of the more serious ones. He, therefore, believes that a simple statement of the fundamental principles underlying the selection of a normal diet may fill a definite need. There are eight chapters dealing respectively with the bulk requirement of the body, the acid-ash type of acidosis, the acetone type of acidosis, the caloric requirement of the body, the protein requirements of the body, the mineral requirement of the body, the vitamin requirement of the body, and the water requirement of the body. Chapter IX is given up to Diet Menus. The book is a common sense one, and free from the fads that characterize the average book on diets.

*The Treatment of Skin Diseases. In Detail.* By NOXON TOOMEY, M.D., B.A., F.A.C.P., Late Instructor in Dermatology, St. Louis University. Volume Three. 512 pages. The Lister Medical Press, St. Louis, 1930. Price, \$7.50.

The methods of treatment described in this book have been adequately experienced by the author in his private and dispensary work of the past fifteen years, and are the methods employed by him at the present time, as they appear to be the most advantageous. In the majority of instances, however, alternative methods are described in order to meet the exigencies of practice in communities where some drugs and some physiotherapeutic facilities are not likely to be immediately available. The book includes an adequate description of the treatment of all known skin diseases. It constitutes Volume Three of the author's "Principles and Practice of Dermatology", the other two volumes being I. Pathology and II. Diagnosis. The author's object has

been to present the therapeutics of skin diseases in a form originating out of his own experience, and the book is no mere rewording of what has been written by others on the subjects treated. In the case of only a very few diseases, mostly tropical, has he been obliged to fall back upon the published observations of other physicians. For those he makes due acknowledgements. The completeness of the discussions and the colloquial manner of treatment are in the author's opinion reasons justifying the publication of this book. In addition it contains some original contributions to the treatment of skin diseases. The claim is made that there is at present no text of like thoroughness on cutaneous therapeutics.

*Recent Advances in Diseases of Children*

By WILFRED P. PEARSON, D S O, M G, D M, F R C P, Physician in Charge of Children's Department, University College Hospital, Physician to Out-patients, Hospital for Sick Children, Great Ormond Street, Sometime Physician to Children's Department, Charing Cross Hospital, and W G WYLLIE, M D, M R C P, Physician to Out-patients, Hospital for Sick Children, Great-Ormond Street, Assistant Physician to Children's Department, Westminster Hospital, Assistant Physician to the Hospital for Epilepsy and Paralysis, Maida Vale. Second Edition, 548 pages, 20 plates and 34 text figures. P. Blakiston's Sons & Co., Inc., Philadelphia, Penna., 1930. Price in cloth, \$3.50.

In this edition practically the same arrangement has been retained as in the first. A certain amount of revision and condensation has, however, been necessary because of the inclusion of new material. The

main additions and alterations are concerned with Postvaccinal and Measles Encephalomyelitis, Chronic Infection of Tonsils and Adenoids, Causation of Cerebral Diplegia, Bronchiectasis, Thoracic Tuberculosis and Asthma, Chronic Abdominal Conditions, Congenital Syphilis, Skin Tests and Some Forms of Immunization. The present book, in spite of its title, is in reality a textbook of children's diseases. The aim of the authors has been to correlate problems of importance in children and adult, and to present investigations more particularly related to the child, in a manner useful to everyday practice, and to visualize children's diseases as a whole. They believe that a bare statement of the results of recent scientific research, as it affects the diseases of children would be both dull and disconnected. The intrusion of personal opinions is intended to be provocative, in order to get away from the habit of taking sets of symptoms—or a syndrome—as an isolated disease, disregarding the fact that many clinical variations may spring from a common basis. If they have systematized children into types unduly, it has been done intentionally, as the factors of "soil" and heredity cannot fail to influence the expression of morbid processes in different types. In order to get a true picture of disease in childhood the authors insist throughout their book that the clinician must have always in mind the grown-up child, the adult. This is a book on children's diseases written with a new and original slant, and, while including recent important additions to scientific knowledge in this field, it offers to the practitioner a consideration of the ailments of the young as they present themselves in every day practice.

## College News Notes

Dr L. J. Moorman (Fellow), Oklahoma City, was elected a member of the Executive Committee of the National Tuberculosis Association during its convention in Memphis, May 8

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At the annual meeting of the American Therapeutic Society at Detroit, June 20-21, Dr Clement R. Jones (Fellow and Treasurer), Pittsburgh, was elected President for the ensuing year

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Dr William C. Voorsanger (Fellow), San Francisco, was elected Representative Director for California of the National Tuberculosis Association, during its last annual meeting

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Dr C. Ray Lounsberry (Fellow), San Diego, addressed the Dermatological Section of the California State Medical Association, which convened at Del Monte the last of May, upon the subject of "Dermatological Neuroses"

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Dr John G. Young (Fellow), Dallas, read a paper before the Dallas Medical Association at Mineral Wells during April on "The Effect of Infection Upon Peristalsis and Appetite with an Outline of Appetite Management"

Dr Young is Chairman of the Dallas County Medical Milk Commission

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Dr L. W. Gehring (Fellow), Portland, addressed the New Brunswick Medical Society at its 50th annual session at St. Andrews-by-the-Sea, June 24-25, on "Syphilis and What is Society's Attitude Toward It"

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Dr Samuel Goldberg (Associate), Philadelphia, was recently appointed Visiting Chief of the Pediatric Department of the Jewish Hospital

Dr Goldberg, with Dr H. Brooker Mills (Fellow) and Dr Kerman Snyder, is the author of a paper entitled "Pyloric Obstruction," which appeared in the April number of Medical Review of Reviews

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Dr Benjamin Hobson Frayser (Fellow), Fort Harrison, Mont., is the author of an interesting article entitled "Medical Fraternities in North America," which appeared in the June Issue of Clinical Medicine and Surgery

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Dr Samuel A. Levine (Fellow), Boston, addressed the Philadelphia Heart Association, May 7, on "A Clinical Conception of the Development of Rheumatic Heart Disease"

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Under the direction of Dr R. R. Snowden (Fellow), the Pittsburgh Diagnostic Clinic held an all-day program of lectures and demonstrations by the staff on April 30. "The subjects discussed were principally those which pertain to problems in diagnoses. Clinical methods and laboratory tests received equal consideration from the staff in an effort to evaluate and present a large number of diagnostic procedures"

Dr Stewart R. Roberts (Fellow), Atlanta, was the invited guest who discussed "The Heart, Gall-Bladder Problem"

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Dr Thomas Klein (Fellow), Philadelphia, has been appointed Professor of Clinical Medicine at Temple University School of Medicine, while Dr Allen G. Beckley (Fellow), Philadelphia, has been appointed Clinical Professor of Medicine

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Dr James Francis Rice (Fellow), Buffalo, is President for 1930-31 of the Buffalo Academy of Medicine. He served as Secretary of the Academy for four years, 1921-25

Dr A B Moore (Fellow), formerly of the Mayo Clinic, is now associated with Doctors Groover, Christie and Merritt in the practice of Roentgenology in Washington, D C Dr Moore has also been appointed Professor of Roentgenology at Georgetown University His Washington address is 1835 Eye St, N W

At the meeting of the American Medical Editors' and Authors' Association at Detroit on June 24, a resolution was adopted, urging legislature to provide for a Department of Health, headed by a medical secretary, in the Cabinet of the President of the United States

Among members of the Board of Governors of the above Society the following members of the College were elected

Dr J M Anders (Master), Philadelphia  
 Dr William Engelbach (Fellow), Santa Barbara  
 Dr T Homer Coffen (Fellow), Portland  
 Dr Julius H Hess (Fellow), Chicago  
 Dr C Ulysses Moore (Fellow), Portland  
 Dr F M Pottenger (Fellow), Monrovia  
 Dr W Forest Dutton (Associate), Amarillo

Dr John Hubeny Maximilian (Fellow), Chicago, is the Managing Editor of RADIOLOGY, the official publication of the Radiological Society of North America Dr Benjamin H Orndoff (Fellow), Chicago, is the Associate Editor, Dr W Warner Watkins (Fellow), Phoenix, is an Assistant Editor, and Dr William B Bowman (Fellow), Los Angeles, Dr L J Carter (Fellow), Brandon, Manitoba, and Dr H Kennon Dunham (Fellow), Cincinnati, are collaborators

Dr Kenneth M Lynch (Fellow), Charleston, is the author of an article entitled "Education Versus Promotion," in the June Issue of the Journal of the Medical Association of Georgia

In the June Issue of the American Journal of the Medical Sciences, the following Fellows contributed articles

Dr Cyrus C Sturgis, Ann Arbor, with  
 Dr M C Riddle, "The Effect of

Single Massive Doses of Liver Extract on Patients with Pernicious Anemia",

Dr Soma Weiss, Boston, with Dr J E F Riseman, "The Symptomatology of Arterial Hypertension",

Dr Edward L Bortz, Philadelphia, "Viceroptosis Its Clinical Significance and Treatment",

Dr Paul A O'Leary, Rochester, with Dr Ruben Nomland, "A Clinical Study of One Hundred and Three Cases of Scleroderma"

Dr Paul F Whitaker (Fellow), Kinston, N C, is the author of a paper on "Bronchiectasis" in the June number of the Virginia Medical Monthly

Under the Presidency of Dr C Lydon Harrell (Fellow), Norfolk, the Norfolk County Medical Society held its annual meeting, June 2

Dr Harrell and Dr Walter B Martin (Fellow), Norfolk, were elected delegates to the next meeting of the Virginia Medical Society

Dr J D Willis (Fellow), Roanoke, is President of the Roanoke Academy of Medicine

Dr Thomas B Fitcher (Associate), Baltimore, was made President-Elect of the Association of American Physicians at their last meeting in May Dr James H Means (Fellow), Boston, was re-elected Secretary

Dr Alfred L Gray (Fellow), Richmond, was recently appointed Councilor of the Southern Medical Association from Virginia, the appointment being made by the President, Dr Hugh S Cumming (Fellow), Washington

Dr Coursen B Conklin (Fellow), Washington, has been re-elected Secretary-Treasurer of the Medical Society of the District of Columbia for the year beginning July 1, 1930

Dr Kenneth M Lynch (Fellow), Charleston, was installed as President of the South



Carolina State Medical Association at its last annual meeting Dr Edgar A Hines (Fellow), Seneca, was re-elected Secretary

The 31st annual meeting of the Association will be held at Greenville, S C

Dr Henry Boswell (Fellow), Sanatorium, Miss, was elected President of the National Tuberculosis Association at its annual meeting at Memphis in May

Dr Stuart Pritchard (Fellow), Battle Creek, was elected one of the Vice Presidents

Under the Presidency of Dr Walter E Vest (Fellow), Huntington, the West Virginia State Medical Association held its annual meeting at White Sulphur Springs, during the latter part of May Dr A H Hoge (Fellow), Bluefield, was elected one of the Vice Presidents for the succeeding year

Dr Vest was elected President of the Alumni Association of the Medical College of Virginia, during the annual meeting in May

Under the Presidency of Dr Henry Green (Associate), Dothan, Ala, the Chattahoochee Valley Medical and Surgical Association held its meeting at Albany, Ga, July 8-9

Dr George R Callender (Fellow), Washington, was elected President of the American Association of Pathologists and Bacteriologists at the last meeting of the Association held in New York

Dr L B McBrayer (Fellow), Southern Pines, has been elected Managing Director of the North Carolina Tuberculosis Association

Dr W S Leathers (Fellow), Nashville, Professor of Preventive Medicine and Dean of the Vanderbilt Medical School, has been elected a member of the Board of Scientific Directors of the International Health Division of the Rockefeller Foundation

Dr Beverly R Tucker (Fellow) Richmond on the occasion of the anniversary of his birth the twenty-ninth anniversary of his graduation in medicine and the fifteenth an-

niversary of the founding of the Tucker Sanatorium, was honored with a dinner given by Dr Howard R Masters and Dr Asa Shield on April 26

Dr Joseph M King (Fellow), Los Angeles, addressed the San Diego County Medical Society, June 10, on "Hypertension"

Dr A J Carlson (Fellow), Chicago, was one of the speakers at the annual dinner of the Faculty and Alumni of Rush Medical College of the University of Chicago at Congress Hotel on June 10 During the meeting, it was announced that Dr Frank Billings had endowed four Fellowships at Rush Medical College in the sum of \$100,000 One of these Fellowships will be named in honor of Dr Ernest E Irons (Fellow), Dean and Professor of Medicine of the Rush Medical School

Dr Thomas B Magath (Fellow), Rochester, was one of the speakers at the meeting of the Twin Lakes District Medical Society of Iowa on June 12

In honor and recognition of twenty-five years of uninterrupted service in the medical school, Dr Charles H Neilson (Fellow), St Louis, was tendered a dinner by the administrative board of St Louis University School of Medicine on June 4 Dr Neilson is Professor of Internal Medicine and Associate Dean of the school

Dr Robert S Berghoff (Fellow), Chicago, was elected President of the Chicago Tuberculosis Society on May 20

Dr James H Hutton (Associate), was installed as President of the Chicago Medical Society at its annual meeting on June 17

Dr Nathan S Davis, III (Fellow), Chicago, was re-elected Secretary

Dr J A Myers (Fellow), Minneapolis, with Dr H D Chadwick, presented a study on childhood tuberculosis before the Michigan Trudeau Society, June 10, at Battle Creek

Dr Mel drum K Welder (Fellow), Albuquerque, was elected President-Elect of the New Mexico Medical Society on June 5

Dr Walter A Bastedo (Fellow), New York, has been elected President of the United States Pharmacopeia Convention

Dr Henry Kennon Dunham (Fellow), Cincinnati, was recently elected President of the Ohio Public Health Association

At the annual meeting of the Pacific Northwest Medical Association at Butte, Mont, June 1-3, papers were presented by Dr A J Carlson (Fellow), Chicago, "Involuntary Nervous System and Circulation", Dr George B Eusterman (Fellow), Rochester, "Significance of Gastric Acidity in General Medicine and Gastro-Enterology", and Dr Allen K Krause (Fellow), Tucson, "Physiological Relations in Tuberculosis"

Dr James D Bruce (Fellow), Ann Arbor, will supervise the work in graduate medicine at the University of Michigan under a new Executive Committee to govern the University of Michigan Medical School, as recently appointed by the board of regents

#### GIFTS TO THE COLLEGE LIBRARY

The following gifts of publications by members to the College Library are duly accepted

Reprint

Dr Douglas Brown (Fellow), Washington, D C, "Arthritis"

Reprint

Dr Philip B Matz (Fellow), Washington, D C, "Future Incidence of Nervous and Mental Disease Among Ex-Service Men"

Reprints

Dr Edwin Schisler (Fellow), St Louis, Mo, "Anesthesia in Cardiac Disease and its Complications"  
"Aneurysms"

Reprint

Dr Leonard F C Wendt (Fellow), Detroit Mich, "Observations on a Summer Camp for Diabetic Children"

Dr Sinclair Luton (Fellow), St Louis, gave "Demonstrations of Interesting Heart Cases" on June 16 at the City Hospital in connection with the program of the Clinical Conference by St Louis Clinics from June 9 to 21

The following Fellows of the College attended the regular scientific conference of St Luke's Hospital Staff on Friday, June 6, at the Union League of Philadelphia

Dr Carl V Vischer, Philadelphia

Dr G Morris Golden, Philadelphia

Dr E J G Beardsley, Philadelphia

Dr Beardsley (Fellow and Governor) was the speaker of the evening

June 6 was the birthday anniversary of the late Dr Carl V Vischer, founder, leader and first Chief Surgeon of St Luke's Hospital, Philadelphia (1896-1906) In honor to Dr Vischer's memory, and as a tribute to his achievements, the scientific program was dedicated

Dr Linn J Boyd (Fellow), New York, is the author of an article, "Symptomatology," which appeared in the June number of the Journal of the American Institute of Homeopathy

The second annual round table of the Physicians Hospital of Plattsburgh, New York, was held August 22-23 Dr William E Robertson (Fellow), Professor of Medicine at Temple University School of Medicine, Philadelphia, gave an address on "The Present Status of Digitalis Therapy, which was discussed by Dr Joseph Wolffe (Associate), Cardiologist at Temple University School of Medicine Dr Edward C Reifstein (Fellow), Professor of Medicine in the College of Medicine, Syracuse University, gave an address on "Some Phases of Syphilitic Heart Disease" Dr Clarence H Beecher (Fellow), Professor of Medicine in the Medical College of the University of Vermont (Burlington), gave a paper on "The Diagnosis of Pericarditis" Dr Carl Wiggers (Fellow), Professor of Physiology, Western Reserve University Medical School (Cleveland), gave the Beaumont Lecture on "The Physiological Meaning of Common Clinical Signs and Symptoms in Cardio-vascular Disease"

#### EIGHTY-FIRST ANNUAL SESSION of the AMERICAN MEDICAL ASSOCIATION

Dr William Gerry Morgan (Fellow) Washington D C was inducted as President of the American Medical Association during the 81st Annual Session at Detroit June 23-27

Dr E Stair Judd of Rochester, Minn, a Fellow of the American College of Surgeons, was made President-Elect

Among Fellows of the American College of Physicians who occupied executive or committee appointments during the Detroit meeting were

#### BOARD OF TRUSTEES

Dr Rock Sleyster, Wauwatosa, Wis

Dr Allen H Bunce, Atlanta, Ga

#### JUDICIAL COUNCIL

Dr J N Hall, Denver, Colo

Dr James B Herrick, Chicago, Ill

#### COUNCIL ON MEDICAL EDUCATION AND HOSPITALS

Dr James S McLester, Birmingham, Ala

Dr M W Ireland, Washington, D C

#### COUNCIL ON SCIENTIFIC ASSEMBLY

Dr Roger S Morris, Cincinnati, Ohio

#### COUNCIL ON PHARMACY AND CHEMISTRY

Dr L G Rowntree, Rochester, Minn

Dr A J Carlson, Chicago, Ill

Dr Ernest E Irons, Chicago, Ill

Dr W McKim Marriott, St Louis, Mo

Dr G W McCoy, Washington, D C

#### COUNCIL ON PHYSICAL THERAPY

Dr Ralph Pemberton, Philadelphia, Pa

Dr A S Warthin, Ann Arbor, Mich

Dr A U Desjardins, Rochester, Minn

Dr Rollin H Stevens (Fellow), Detroit, was Chairman of the local Committee on Arrangements for the Detroit Session

Dr L G Rowntree (Fellow), Rochester, Minn, delivered a clinical lecture on "Arthritis" during the opening day. To the regular program for the Section on Practice of Medicine, the following Fellows contributed, Dr Torald Sollman, Cleveland, Dr Philip S Hench, Rochester, Minn, Dr Ralph Pemberton, Philadelphia, Dr L M Warfield, Milwaukee, "Hypothyroidism," Dr T L Squier, Milwaukee, Dr C N Hensel, St Paul, Dr James B Herrick, Chicago, "The Clinical Signs of Heart Disease, with Particular Reference to Etiology," Dr Sinclair Luton, St Louis, Dr Emanuel Libman, New York, Dr M W Ireland, Washington, Dr Charles H Lawrence Jr, Boston, "The Significance and Treatment of Men-

strual Disorders in Adolescent Girls," Dr C J Marinus, Detroit, Dr O W Bethea, New Orleans, "The Treatment of Pneumonia," Dr A E Greer, Houston, Dr Ernest E Irons, Chicago, Dr Henry W Woltman, Rochester, "Tumors Involving the Spinal Cord", Dr Stewart R Roberts, Atlanta, "Agranulocytic Angina," Dr J E Talley, Philadelphia, Dr Herbert Z Giffin, Rochester, Dr James S McLester, Birmingham, "Clinical Syndromes That Include Achlorhydria," Dr O H Petty, Philadelphia, Dr C C Bass, New Orleans, "The Treatment of Malaria, with Some Reference to Recently Promoted New Remedies," Dr E R Whitmore, Washington, Dr Joseph L Miller, Chicago, the Frank Billings lecture on "The Present Status of Nonspecific Therapy", Dr George B Eusterman, Rochester, Dr H L Bockus, Philadelphia, Dr G G Richards, Salt Lake City, Dr Willard J Stone, Pasadena, "Dietary Facts, Fads and Fancies", Dr Harlow Brooks, New York, Dr F G Brigham, Boston, and Dr S S Altshuler (Associate), Ann Arbor

Many members of the American College of Physicians also contributed to other programs than that of the Section on Practice of Medicine. To the Section on Surgery, Dr A C Ivy (Fellow), Chicago, gave a paper on "Physiologic Disturbances Incident to Jaundice." Dr George E Pfahler (Fellow), Philadelphia, discussed the paper on "The Use of Radium and High Voltage Roentgen Therapy in Conjunction with Radical Operation for Cancer of the Breast"

In the Section on Obstetrics, Gynecology and Abdominal Surgery, Dr J A Myers (Fellow), Minneapolis, discussed the paper on "The Changes in the Mammary Glands of the Pregnant Albino Rat Deprived of Vitamin E." Dr William Duncan Reid (Fellow), Boston, contributed a paper on "The Heart in Pregnancy." Dr George R Herrman (Fellow), New Orleans, with Dr F L King, gave a paper on "Heart Disease and Pregnancy." Dr A J Carlson (Fellow), Chicago, discussed the paper on "Pupillary Reactions as a Diagnostic Aid in Pregnancy."

In the Section on Ophthalmology, Dr Gerald B Webb (Fellow), Colorado Springs, discussed "The Eye in the Tuberculous Patient."

In the Section on Diseases of Children, Dr Hugh S Cumming (Fellow), Wash?

ton, reported on "The White House Conference on Child Health and Protection" Dr C C McLean (Fellow), Birmingham, delivered a paper on "The Recurrent Incidence of Respiratory Infections of Childhood" Dr J A Myers (Fellow), Minneapolis, discussed the paper on "The Significance of Advanced Tuberculous Infection in School Children"

In the Section on Pharmacology and Therapeutics, Dr Roger I Lee (Fellow), Boston, was a member of the Executive Committee Dr Soma Weiss (Fellow), Boston, delivered a paper on "The Treatment of Arterial Hypertension" Dr Paul Dudley White (Fellow), Boston, gave a paper on "The Treatment of Edema by Mechanical Means," this paper being later discussed by Dr Alpheus F Jennings (Fellow), Detroit Dr Cyrus C Sturgis (Fellow), Ann Arbor, with Dr Raphael Issacs, gave a paper on "Treatment of Pernicious Anemia with Dried Stomach" Dr Herbert Z Griffin (Fellow), Rochester, with Dr Charles H Watkins, gave a paper on "Clinical Results in the Treatment of the Various Types of Secondary Anemia," this paper being discussed by Dr A B Brower (Fellow), Dayton Dr Philip S Hench (Fellow), Rochester, delivered a paper on "Unusual Reactions to Protein Therapy" Dr Ernest E Irons (Fellow), Chicago, discussed the paper by Doctors Cecil and Plummer on "Pneumococcus Type 1 Pneumonia, with Especial Reference to Serum Treatment" Dr A J Carlson (Fellow), Chicago, discussed the paper by Doctors Van Dyke and Wallen-Lawrence on "The Growth Promoting Hormone of the Pituitary Body"

In the Section on Pathology and Physiology, Dr A H Sanford (Fellow), Rochester, was Chairman, Dr A C Ivy (Fellow), Chicago, Vice Chairman and Dr J J Moore (Fellow), Chicago, Secretary Dr Aldred Scott Warthin (Master), Ann Arbor, gave a scientific exhibit on "The Pathology of Syphilis of the Heart and Aorta" Dr Howard T Karsner (Fellow), Cleveland, gave a lantern demonstration on "Pathology of Endocarditis" Dr A H Sanford (Fellow), Rochester, delivered the Chairman address on "Role of the Clinical Pathologist" Dr William Carpenter MacCarty (Fellow), Rochester, gave a lantern demonstration on "Principles of Prognosis in Cancer" Dr

John V Barrow (Fellow), Los Angeles, gave a motion picture demonstration of "Characteristics and Pathology of Human Intestinal Protozoa" Dr Sidney K Simon (Fellow), New Orleans, Dr Kenneth M Lynch (Fellow), Charleston, and Dr Frank Smithies (Master), Chicago, discussed Dr Barrow's demonstration and paper Dr Samuel M Feinberg (Fellow), Chicago, delivered a paper on "The Uses and Limitations of Skin Tests in Allergy," this paper being discussed by Dr W T Vaughan (Fellow), Richmond, and Dr W W Duke (Fellow), Kansas City Dr A C Ivy (Fellow), Chicago, discussed the lantern demonstration and paper by Doctors Mann and Bollman on "The Reaction of the Contents of the Gastro-Intestinal Tract" Dr E R Whitmore (Fellow), Washington, was one of the discussants of the paper, "Chemical Studies of Malignant Conditions"

In the Section on Nervous and Mental Diseases, Dr George W. Hall (Fellow), Chicago, was Chairman, Dr Laurence Selling (Fellow), Portland, was Vice Chairman, Dr Walter Freeman (Fellow), Washington, was Secretary, and Dr Lewis J Pollock (Fellow), Chicago, and Dr George W Hall (Fellow), Chicago, were members of the Executive Committee Dr W H Riley (Fellow), Battle Creek, discussed the paper on "Influence of Emotional Shock on the Gastro-Intestinal Tract in the Psychoneuroses" Dr James L McCartney (Fellow), Hartford, delivered an address on "Psychiatric Consultation Service Supplied by the State Department of Health" Dr William C Menninger (Fellow), Topeka, gave a paper on "Juvenile Dementia Paralytica A Study of Forty Cases," which paper was discussed by Dr Hans Reese (Fellow), Madison, Dr Henry W Woltman (Fellow), Rochester, and Dr Paul A O'Leary (Fellow), Rochester

In the Section on Dermatology and Syphilology, Dr Francis E Senear (Fellow), Chicago, acted as Secretary Dr Paul A O'Leary (Fellow), Rochester, was the discussant of the paper on "Syphilis of the Central Nervous System in Infants and Children" Dr Maximilian A Ramirez (Fellow), New York, with Dr J J Eller, gave a paper on "Intradermal, Scratch Indirect and Contact Tests in Dermatology Comparative Study"

In the Section on Preventive and Industrial Medicine and Public Health, Dr Francis M Pottenger (Fellow), Monrovia, discussed the paper on "Racial Susceptibility to Tuberculosis" Dr William Engelbach (Fellow), Santa Barbara, presented a paper on "Normal Weight and Measurements from Birth to the Age of Twenty"

In the Section on Orthopedic Surgery, Dr Ralph Pemberton (Fellow), Philadelphia, gave a lantern demonstration of "Developments in the Problem of Arthritis"

In the Section on Gastro-Enterology and Proctology, Dr Julius Friedenwald (Fellow), Baltimore, acted as Chairman, and Dr A F R Andresen (Fellow), Brooklyn, as Secretary Dr John A Lichty (Fellow), Clifton Springs, gave a lantern demonstration on "The Present Care and Consideration of the Colon," which paper was discussed by Dr Sara M Jordan (Fellow), Boston, and Dr John G Mateer (Fellow), Detroit Dr Frank Smithies (Master), Chicago, gave a lantern demonstration, "From Medical Standpoint" in connection with the symposium on acute intestinal obstruction Dr Charles Eastmond (Fellow), Brooklyn, gave a lantern demonstration in the same symposium, "From Roentgenologic Standpoint" Dr Anthony Bassler (Fellow), and Dr J Raymond Lutz (Fellow), both of New York, presented a paper on "Sprue Diagnosis and Treatment" Dr Samuel Weiss (Fellow), New York, gave a motion picture demonstration on "A New Gastro-scope" Dr George B Eusterman (Fellow), Rochester, gave a lantern demonstration on "The Incidence and Diagnosis of Gastro-Intestinal Syphilis," in connection with the symposium on gastro-intestinal syphilis Dr Leon T LeWald (Fellow), New York, gave a lantern demonstration in the same symposium on "Roentgen Diagnosis of Gastric Syphilis" Dr Paul A O'Leary (Fellow), Rochester, gave a clinical study on 'Syphilis of the Liver' Dr Julius Friedenwald (Fellow), Baltimore, gave the Chairman's address on "The Human Constitution in Its Relation to Gastro-Intestinal Diseases" Dr Quinter Olen Gilbert (Fellow), Oakland, gave a lantern demonstration on 'Some Evaluations of Gastro-Intestinal Motility.' Dr Martin F Robbess (Fellow), Philadel-

phia, offered a lantern demonstration on "Acid Combining Values of Foods," which paper was discussed by Dr A C Ivy (Fellow), Chicago, and Dr Elmer L Eggleston (Fellow), Battle Creek Dr A J Carlson (Fellow), Chicago, was a discussant of the paper on "Mechanisms of Gallbladder Contraction and Evacuation" Dr H L Bockus (Fellow), Philadelphia, with Doctors Shay, Pessel (Fellow) and Willard, gave a lantern demonstration on "Diagnosis of Cholelithiasis Stressing the Relative Value of Nonsurgical Duodenal Drainage (Lyon Technique) and Cholecystography"

To the Section on Radiology, Dr William B Bowman (Fellow), Los Angeles, acted as Vice Chairman, Dr George W Grier (Fellow), Pittsburgh, as Secretary, and Dr M J Hubeny (Fellow), Chicago, as a member of the Executive Committee Dr A U Desjardins (Fellow), Rochester, gave a paper on "Radiotherapy for Inflammatory Conditions," which paper was discussed by Dr Rollin H Stevens (Fellow), Detroit Dr Henry J Ullman (Fellow), Santa Barbara, was the discussant of a paper on "Irradiation of Mammary Cancer, with Especial Reference to Measured Tissue Dosage" Dr George E Pfahler (Fellow), Philadelphia, with Dr J H Vastine, gave a scientific exhibit on "Radium Therapy in Cancer of the Mouth with Especial Reference to the Newer Technic", this paper was discussed by Dr George W Grier (Fellow), Pittsburgh Dr Albert Soiland (Fellow), Los Angeles, was one of the discussants of the lantern demonstration on "Indications and Limitations for Intensive Roentgen-Ray and Radium Treatment of Advanced Cancer" Dr Soiland also gave an address on "Cancer Treatment" Dr A B Moore (Fellow), Washington and Dr B R Kirklin (Fellow), Rochester, gave a paper on "Roentgenologic Diagnosis of Diaphragmatic Hernia" Dr Sinclair Luton (Fellow), St Louis, gave a lantern demonstration on the "Enlarged Heart Its Detection and Significance," this paper being discussed by Dr Leon T LeWald (Fellow), New York Dr LeRoy Sante (Fellow), St Louis, was the discussant of the paper on 'The Roentgen Diagnosis of Small Pleural Effusions with Observations of the Movement of Pleural Effusions'

## OBITUARY

Doctor William Colby Rucker

In the untimely passing of Dr W C Rucker (Fellow), May 23, 1930, the United States Public Health Service, the medical profession and the country at large loses an important figure in the field of medicine and sanitation. Dr Rucker was comparatively a young man, at the peak of an active and progressive career, whose personality, scholarly attainments, executive and administrative ability gained for him an enviable reputation in varied fields. He was an indefatigable student, possessing a mind given to research and investigation. He was an author, a poet, a good clinician and possessed a subtle sense of humor which made his labors pleasurable and endeared him to all those with whom he came in contact. He contributed many articles and bulletins on public health subjects covering original work in epidemiology of the communicable diseases.

He was born on September 28, 1875, received his education at the University of North Dakota and the University of Minnesota where he was graduated in 1894. His medical degree he obtained from Rush Medical College at Chicago, Ill. He experienced a short period as commissioned officer in the Medical Corps of the United States Navy and in 1902 was given a commission in the United States Public Health Service. He received the degree of Doctor of Public Health at Stanford University, was a charter member of the Board of National Medical Examiners, and had the distinction of being both a Fellow of the American College of Surgeons and

the American College of Physicians. As a sanitarian his reputation was international. He made many sanitary surveys in both Central and South America, played a leading and dominant part in the campaign against yellow fever in New Orleans in 1904 and was at that time a victim of the disease. In 1906, working with Dr Rupert Blue in San Francisco, California, he conducted a splendid campaign against bubonic plague. While recuperating from this strenuous work, Dr Rucker discovered, working with others, that squirrels could also transmit plague. In 1911 he was again a leading figure in the campaign against spotted fever at Victor, Montana. During the World War he was detailed to the American Expeditionary Forces where he did most creditable work and served until June, 1919. He was the first Chief Medical Advisor of the Bureau of War Risk Insurance at Washington, D C, and helped to organize this department into an efficient organization. From 1920 to 1924, he was Chief Quarantine Officer of the Panama Canal. In 1925 he was detailed as Medical Officer In Charge of the United States Marine Hospital at New Orleans, La., at which hospital he served until his death.

Dr Rucker developed into an extremely capable hospital head, was highly respected by the State and City hospital organizations and contributed heavily toward the organization of hospital superintendents. His pen was prolific in a wide range of non-technical subjects and his book entitled "Leadership" written largely for Serv-

ice officers, is accepted as a catechism for young officers entering the Service. He kept abreast with the medical profession of his time and rarely overlooked attending any type of medical gathering. He was 1st Vice President of the Association of Military Surgeons of the United States, a valued member of the editorial board of THE MODERN HOSPITAL and contributed consistently over a period of many years to this magazine.

His life was an inspiration to young officers in the United States Public Health Service and his *esprit de corps* advanced the Service which was so dear to him.

(Furnished by Randolph Lyons, M D, F A C P, Governor for Louisiana, through data furnished by William Y Hollingsworth, M D, and Waldemar R Metz, M D)

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Dr Guy Lincoln Kiefer (Fellow), Lansing, Mich, died May 8, 1930, of angina pectoris, aged 63 years.

Dr. Kiefer received his A B and A M degrees from the University of Michigan, and later his M D degree from the same institution, 1891. In 1911, his Alma Mater conferred the honorary degree of Doctor of Public Health upon him.

During a long useful service, Dr Kiefer served as County Physician of Wayne County, City Physician of Detroit, Professor of Preventive Medicine and Public Health at the Detroit College of Medicine and Surgery, Chairman of the Section on Preventive Medicine and Public Health of the American Medical Association and Vice Chairman of the Section on Pub-

lic Health Administration of the American Public Health Association.

He was an Ex-President of the Michigan State Medical Society and of the Wayne County Medical Society, a Fellow of the American Medical Association and had been a Fellow of the American College of Physicians since 1917.

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Dr William J Kay (Fellow), Lapeer, Mich, died April 16, 1930, of streptococcic sore throat, aged, 63 years.

Dr Kay was born at Belmore, Ontario, and received his preliminary education at the Harriston Collegiate Institute. He graduated in medicine from the Detroit College of Medicine and Surgery in 1897. For several years, he has been Consulting Internist and Medical Superintendent of the Michigan Home and Training School. He was a member of Lapeer County Medical Society, an Ex-President of the Michigan State Medical Society, a Fellow of the American Medical Association and had been a Fellow of the American College of Physicians since 1919.

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Dr Robert Pollock (Fellow), San Diego, Calif, died, June 2, 1930, aged 64 years.

Dr Pollock was a graduate of the Western Reserve University School of Medicine, 1892, and interned at the Cleveland City Hospital in 1892-93. He went to San Diego nineteen years ago. His health, which had not been good, returned and he again took up active practice and played an important part in bringing medicine to a high position in San Diego. He was

active in his local medical societies, had acted as a delegate to state and national organizations and was an Ex-President and member of the Board of Governors of the Southern California Medical Association. His untiring effort lives as a monument in the San Diego Medical Library for which he did so much. His good counsel and earnest efforts for better medicine will be missed. The medical profession in California and the citizens of his community will miss a loyal citizen and a good physician.

(Furnished by Egerton Crispin, M.D., F.A.C.P., Governor for Southern California)

Dr. Antonio D. Young

On June 3, 1930, the State of Oklahoma suffered a distinct loss through the death of one of its most useful citizens. Removed from the turmoil of traffic, on a shaded street, in the upper chamber of his quiet home, Dr. Antonio D. Young died, as he had lived, with commendable courage and composure.

Here was a man who loved his fellow men and though he lived well within the plane of their comprehension he was set apart as the kindly physician. While highly trained and peculiarly skilled in his chosen specialty he never lost sight of the fact that sick people need a physician with a practical knowledge of the human body, who is willing to sit at the bedside and bring to bear a sympathetic, intelligent application of this knowledge to the patient's individual needs.

Dr. Young possessed a radiant personality, to look into his eyes, to receive his genial smile, to hear his voice

and shake his hand was enough to send one joyfully on his daily round of duties.

Though by no means a recluse he avoided fame, always insisting upon remaining on his accustomed level, where with simplicity and gentleness he enveloped all with his tolerant insight and sympathetic understanding, saturating his environment with the most delicate wit and humor.

In closing this memorial we can think of nothing more appropriate than the following from Maurice Maeterlinck: "Our dead are greater and more truly alive than we are, when we forget them it is our whole future that we lose sight of, and when we fail in respect to them it is our immortal soul that we are trampling under our feet."

Dr. Young was born in Jerseyville, Ill., December 11, 1873, and graduated from the Jerseyville High School in 1892. He graduated at Barnes Medical School, St. Louis, Mo., in 1895, and practiced medicine at Downs, Ill., until he came to Oklahoma City, February, 1901. He was married to Elberta Meyer, December 1, 1897.

Dr. Young was secretary of the faculty of the Medical Department of Epworth University which later became the Medical Department of the Oklahoma State University. He was professor of Neurology in the latter school from the date of its organization.

Dr. Young served in the World War from March 1918 to 1919.

He was a Fellow of the American College of Physicians, a member of the American Medical Association, the Southern Medical Association, the Oklahoma State and County Associations.



and the Oklahoma City Academy of Medicine. He was a charter member of the latter and helped write its constitution. He was also a member of the Men's Dinner Club and was closely identified with various social and outdoor clubs.

(Furnished by Lea A. Riely, M.D., F.A.C.P., Governor for Oklahoma.)

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Dr. Frank Canfield Hollister (Associate), New York, N.Y., died suddenly November 30, 1929, aged 64.

He was a graduate of the Bellevue Hospital Medical College, Class of 1890.

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Dr. J. Edward Harbinson (Fellow), Woodland, Calif., died during April, 1930. Dr. Harbinson was born, April 28, 1895, in Yolo County (California), and was educated in the Sacramento Public Schools. He received his Degree of Bachelor of Science in the University of California in 1917, and his Degree of Doctor of Medicine from the same institution in 1922. He was Intern and Assistant Resident Physician at the University of California Hospital during 1922 and 1923, and then became Physician in Chief at the Woodland Clinic Hospital, which appointment he held until the time of his death.

Dr. Harbinson contributed numerous scientific articles to medical literature, these articles dealing chiefly with the use of Ammodoxyl Benzoate in the

treatment of Arthritis and Undulant Fever.

He was a member and Ex-President of the Yolo-Colusa County Medical Association, a Fellow of the American Medical Association, a member of the California State Tuberculosis Association, and was elected a Fellow of the American College of Physicians on October 27, 1929.

Dr. Joseph McIntyre Patton (Fellow), Chicago, Ill., died, April 16, 1930, of chronic myocarditis, arthritis and arteriosclerosis, aged, 69.

Dr. Patton was born at Ralston, Pennsylvania, received his preliminary education at Hasbrouck's Institute of Jersey City and graduated from the Medical Department of the University of the City of New York in 1882. He was Professor Emeritus of Clinical Medicine at the University of Illinois, College of Medicine, and in earlier years was Professor of Physical Diagnosis in the College of Physicians and Surgeons of Chicago. Dr. Patton was the author of a long list of publications, which appeared in the leading medical journals of the country. He was author, also, of two books, "Clinical Lectures on Heart, Lungs and Pleura" and "Anesthesia and Anesthetics." He was a Fellow of the American Medical Association, a member of the Illinois State Medical Society, a former President of the Chicago Medical Society, and had been a Fellow of the American College of Physicians since 1920.

# The Effect of General Systemic Arteriosclerosis Upon the Heart and the Systemic Circulation\*†

By GEORGE FAHR AND JAY DAVIS, *Minneapolis, Minn*

IT cannot be said that all of the factors possibly associated with the development of chronic non-valvular heart disease have been adequately investigated. We have very good evidence that long continued high blood pressure will lead to failure of the left ventricle. We also know that arteriosclerosis of the coronary arteries leads to thrombosis and infarction of the heart with sudden death or acute onset of heart failure. Coronary sclerosis also very frequently leads to chronic heart failure through inadequate blood supply to the heart muscle. In as far as we are aware, the effect of generalized arteriosclerosis upon the work of the heart, upon the flow of blood through the systemic and coronary circulations, and upon the size of the heart has not been adequately studied by anyone. Romberg<sup>1</sup> believes that the work of the left ventricle is enormously increased in changing from an arterial system with slight rigidity to an arterial system with great rigidity, and that therefore

the work of the left ventricle must be increased in generalized arteriosclerosis. We have never been able to find a detailed description of Romberg's method and his experimental results.

Romberg's assistant Lange<sup>2</sup> has weighed hearts in cases of generalized arteriosclerosis and found little or no increase in weight, a bit of evidence which would seem to point to arteriosclerosis as no factor in increasing the work of the left ventricle.

After a brief survey of the field, we were convinced that a systematic investigation of the hemodynamics of arteriosclerosis was needed. We shall report today on the results of our preliminary investigation in this field. In this paper we shall consider arteriosclerosis as an increase in the rigidity of the arterial system down to the capillary area. Any decrease in the effective lumen of this system would lead to high blood pressure and will not be considered in this paper. By means of an analytic study of the problem, we feel that we have made it seem very probable that a marked degree of generalized systemic arteriosclerosis will not increase the work done by the left ventricle<sup>3</sup> provided the blood pressure does not rise. In

\*Presented before the American College of Physicians, Minneapolis, Minnesota, February 11, 1930.

†From the Department of Medicine of the University of Minnesota and the Minneapolis General Hospital.

order that this latter condition be realized, we must provide that the arteriosclerosis or increased rigidity of the arterial system be produced in such a way that lumen changes are not produced at the same time that rigidity changes are produced

For all practical purposes the work which the left ventricle performs can be expressed in the form of an integral

$\int_{p_0}^{p_1} P \Delta v$  which says that the work of the left ventricle is equal to the summation of the various small amounts of blood that are put out in a small time interval from the beginning of systole to the end of systole and against a blood pressure which rises from the diastolic to the systolic value. If the minute volume is kept constant, it can be easily seen that the only other factor in the work of the heart is the blood pressure. If we therefore keep the mean blood pressure constant or the systolic blood pressure constant, it can be easily seen even by the mathematical uninitiated that the work of the heart in arteriosclerosis is not going to be much greater than that in the normal condition so long as we assume that the output of blood from the heart per beat delete remains the same.

Making use of the data obtained by A. V. Hill<sup>1</sup> and the curve showing the relation between volume of the arterial system and blood pressure developed by Hill in his work, I have been able to integrate the work formula of the heart both for the normal artery and an artery with the rigidity three and a half times the normal. This integration shows that the work

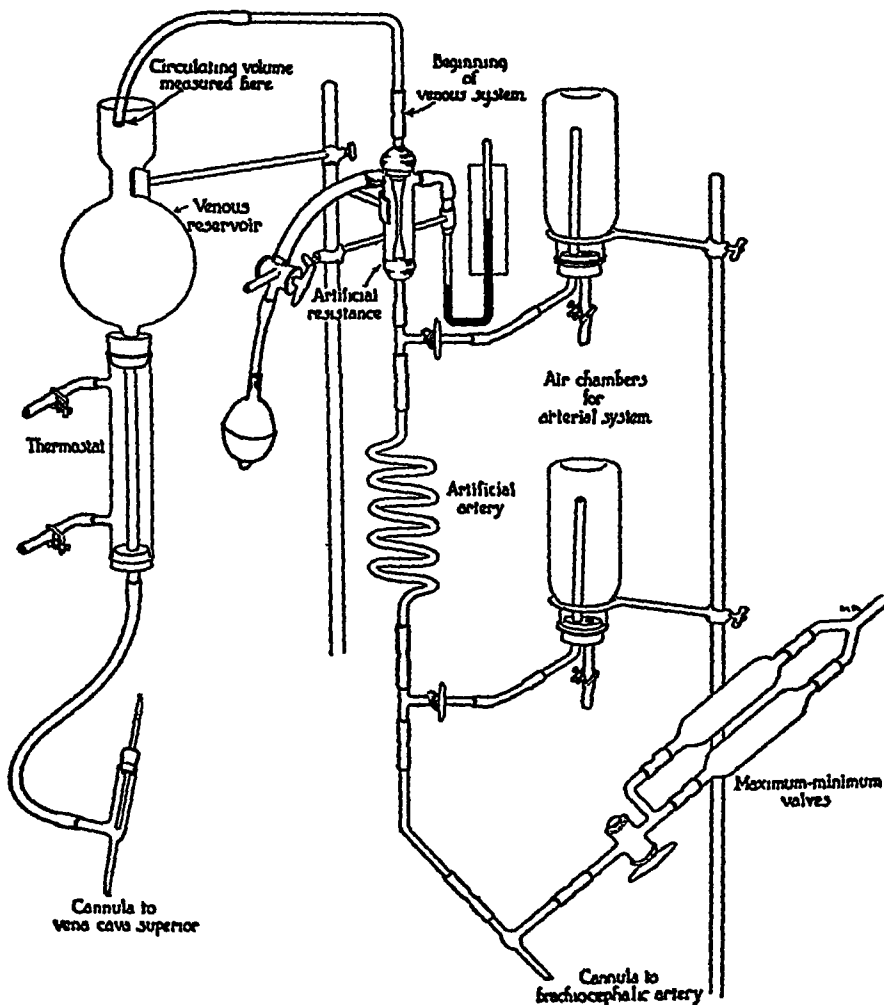
of the heart is just about the same in arteriosclerosis as in the normal condition, provided the output per beat remains the same and the arithmetical mean blood pressure remains the same. In this analytical method of attacking the problem, there was one factor about which we know nothing and which could not be taken into consideration, namely the "run off" from the arterial system. By making assumptions as to the time relations of the run-off, the A. V. Hill curve for the relation between volume of the artery and blood pressure could be reconstructed and then integrated, but this method was so full of assumptions that we believed it to be more convincing to work experimentally upon this problem. We have now finished our preliminary experiments and we can state definitely that if the minute volume of blood flow is kept constant and the arithmetical mean pressure remains the same, a very enormous degree of rigidity of the artery does not increase the work of the left ventricle. Moreover, we can state that under the given conditions the output of blood through the systemic circulation remains practically the same when the rigidity of the arterial system is increased many times. There is no dilatation of the heart in arteriosclerosis and the only adverse factor that we have so far been able to make out is a slight reduction of the flow of blood through the coronary arteries of the dog's heart in arteriosclerosis in some of our experiments.

A brief description of our experimental method is necessary for an understanding of the way in which the

problem was solved and will be given here

The heart of the dog in a Starling Heart-Lung Preparation was used as pump. A cannula was inserted in the arch of the aorta of this heart, all arterial branches were ligated so that blood pumped out of the left heart was all forced through the cannula which was connected to a manometer and a system of tubes which emptied into a venous reservoir connected to the superior vena cava. The inferior vena cava was ligated. All the blood entering the superior vena cava from the reservoir passed into the right

auricle, hence to right ventricle and through the lungs to the left ventricles. (See figure 1.) An artificial resistance is inserted in the arterial system, by means of which the blood pressure can be adjusted to any desired height and kept constant. The greater part of the arterial system consists of a coiled glass tube, with side tubes, provided with cocks and leading into two bottles each of 1,000 cc. capacity. When the passage to these bottles is closed the arterial system has a very high degree of rigidity, approximately 10 times the volume rigidity of the normal human arterial system as de-



terminated by A. V. Hill et al. This degree of rigidity is much higher than the greatest rigidity measured by Hill on an old man with arteriosclerosis. The glass tube is of course extremely rigid. The manometer for measuring blood pressure and the artificial resistance are the only parts of the system that expand under pressure. In all measurements of the coefficient of volume elasticity of the arterial system, the artificial resistance and manometer were included. When the two cocks are opened the arterial system has two large air chambers which reduce the rigidity of the system to about one half the rigidity of a normal human arterial system, as determined by A. V. Hill. We were thus able to turn arteriosclerosis on and off at will by turning the stop cocks.

It has been shown by Starling and Vischer<sup>5</sup> that the diastolic volume of the heart is accurately proportional to the energy developed by the heart during each beat; that is the work of the heart per beat is determined exactly by the diastolic size of the heart; or in other words the diastolic volume of the heart is an accurate measure of the work of the heart provided the condition of the heart muscle remains constant. If the heart dilates more work is being done, if the diastolic volume gets smaller, less work is being done. In our experiments, the heart was enclosed in a cardiometer connected to a recording tambour designed by Wiggers. The tambour lever records the slightest variation in diastolic volume of the heart and thus indirectly records the work of the heart. If the heart does not dilate

when the stop cocks are closed and the arterial system is rigid (arteriosclerosis) then we can be sure that this degree of arteriosclerosis does not increase the work of the left ventricle.

In addition we measured the volume flow of blood in the system circulation by allowing the blood from time to time to flow into a graduated cylinder. A stop watch graduated in 1/10 seconds was used to measure the time taken to fill the cylinder with a measured volume of blood. The minute flow could then be calculated. In this way the systemic minute flow in the rigid and non-rigid system could be measured with an accuracy of 5%. Moreover the cardiometer was calibrated by injecting a known quantity of air into the cardiometer and measuring the movement of the lever. We could then determine with some degree of accuracy the stroke output of the heart. In only one experiment did this value seem much too small, though in general this method of measuring stroke output is known not to be very accurate. Knowing stroke output, rate of the heart, and the systemic minute flow, the coronary flow is easily calculated. The rate of the heart remains constant in the rigid as well as non-rigid state, but because of the possible inaccuracy in the stroke output measurement, we do not lay much stress on our coronary flow figures. These must be checked by actual measurement in the future.

We append a selection from our experimental results to show that the work of the left ventricle is not increased during arteriosclerosis (rigid

*Experiment of April 16, 1929*

Rigidity of our material system with air chamber connection (normal) is  $\frac{1}{3}$  that of A. V. Hills "mean normal" human artery

Rigidity of our arterial system without air chamber connection is 66 times "mean normal" human artery

Ergo our system without air chamber connection is 20 times the rigidity with air chamber connection

	Without Air Chamber (Arteriosclerosis)	With Air Chamber (No arteriosclerosis)
Sys B P.	246)	224)
	) 120	) 66
Dias B P	126)	158)
Stroke Vol	122	127
Minute Vol	1220 Rate 100	1270
Circul Vol	857 cc	833 cc.
Coronary flow	363	437

The heart was about 1-1.5 cc smaller in diastole when air chambers were not connected with arterial system, ergo no increase in work of heart in the more rigid arterial system. In fact less work was done in arteriosclerosis because stroke output and mean pressure were less. During the experiments with air chamber connected the flow from the tube leading into venous reservoir was steady with only a slight pulsation. During the experiments without the air chambers (arteriosclerosis) the blood spurted in jets from the end of the tube leading into reservoir. In some of our experiments the flow had nearly ceased at the end of diastole.

*Experiment of October 15, 1929*

Rigidity of arterial system with air chamber connected (normal) is  $\frac{2}{3}$  that of A. V. Hills "mean normal" human artery

Rigidity of arterial system without air chamber connection (arteriosclerosis) is 10 times the rigidity of the "mean normal" human artery as determined by A. V. Hill

Ergo the rigidity in our arterial system without air chamber connection is 15 times that of the arterial system with air chamber connected

	(Arteriosclerosis)	(No arteriosclerosis)	
	126)	122)	{
Sys B P	) 64	) 50	
Dias B P	62)	72)	
Stroke Vol	75 cc	78 cc.	
Minute Vol	937 cc	975 cc	
Circul Vol	893 cc Rate 125	857 cc	
Coronary flow	44 cc.	118 cc	

Heart was dilating continuously from start of this set of experiments. Apparently no difference in diastolic volume without air chamber and with air chamber in arterial system.

*Experiment of Dec 30, 1929*

Rigidity of our arterial system with air chamber connection (normal) is  $\frac{3}{4}$  the rigidity of A. V. Hills "mean normal" artery

Rigidity without air chamber (arteriosclerosis) is 9 times the rigidity of the human arterial system as determined by A. V. Hill

Ergo rigidity in this artificial arteriosclerosis is 12 times the rigidity in the condition approximating normal.

With Air Chamber (Normal)		Without Air Chamber (Arteriosclerosis)	
Systolic B P.	206)	192)	
	) 128	) 88	
Diastolic B P.	83)	104)	
Circul. Vol	1915 cc	2000 cc	
Stroke Vol	14.4 cc ?	14.2 cc ?	
Rate of Heart	100	100	
Minute Volume	1440 cc ?	1420 cc ?	
Coronary Flow	—	—	

Diastolic volume is 0.8 cc. less without air chamber than with air chamber. In other words no increase in volume but rather a slight decrease in the condition of increased rigidity. Cardiometer values for stroke volume of heart are much too low. Probably due to improper position of cardiometer on heart. Minute volume must be about 2400 cc. This heart is doing nearly as much work as the heart of an athlete in severe exertion. The minute volume as well as the blood pressure is increased beyond the normal. Even under these circumstances the heart does not dilate during the period when it is pumping through the rigid system nor is the volume of the systemic circulation reduced.

system), and that the systemic minute volume remains practically constant whether the heart pumps into a very rigid arterial system or into a system which has air chambers.

These experiments prove that increased rigidity of the arterial system without changes in the diameter of the system causes no increase in the work of the left ventricle in expelling blood into and along the more rigid arterial system. In other words arteriosclerosis not associated with increased blood pressure causes no increase in the work of the left ventricle.

These experiments also prove that the volume flow of blood in a more rigid arterial system is as great as in a less rigid system. In other words arteriosclerosis not associated with narrowing of the lumen of the arterial system is not detrimental to the volume flow of blood.

It is possible that severe generalized arteriosclerosis may lead to a reduction in volume flow through the coronary arteries and thus aid in bringing on circulatory failure when the coronary arteries are already narrowed from severe coronary arteriosclerosis.

## REFERENCES

- <sup>1</sup>ROMBERG: Lehrbuch der Krankheiten des Herzens.
- <sup>2</sup>F. LANGE: Verhandlungen d. Deutsch. Gesellschaft f. Innere Medizin. 1928. 433.
- <sup>3</sup>GEORGE FAHR: Proceedings of the Society of Experimental Biology and Medicine. 1927. V. XXIV, 405.
- <sup>4</sup>A. V. HILL, J. C. BRAMWELL, A. C. DOWNING. Heart, 1923, X, 289.
- <sup>5</sup>E. H. STARLING and M. B. VISCHEK. Journal of Physiology. V 1927, LXII, 243.

# Some Newer Aspects in the Problem of Essential Hypertension\*

NORMAN M. KEITH, M D., *Division of Medicine*, and  
JAMES W KERNOHAN, M B. *Section on Pathologic Anatomy*,  
*The Mayo Clinic, Rochester, Minnesota*

**B**RIGHT, 100 years ago, showed that there was a relationship between pathologic changes in the kidney and diffuse vascular disease. Forty years later, Johnson, Gull, and Sutton demonstrated in cases similar to those cited by Bright that there might also be injury to the peripheral vessels including the arterioles. Thirty-five years ago Allbutt showed clinically and pathologically that diffuse vascular disease with hypertension, without renal lesions, and without gross peripheral vascular lesions, could exist.

Since that time, of course, many observers have wondered as to the cause of hypertension, and there have been theories that the thyroid gland and the suprarenal gland were involved. In the last few years certain anatomic conditions of the vascular system have been recognized as being associated with hypertension. Much has been learned concerning the diagnostic and prognostic significance of retinal vascular changes. Moreover, certain rare conditions of the vascular system have come to be recognized as causative of

hypertension. These include arteriovenous aneurysm and congenital stenosis of the isthmus of the aorta.

There are eight types of hypertension. The first is the hypertension of arteriovenous aneurysm; the second that associated with congenital stenosis of the aorta. Third, is the hypertension that occurs in hyperthyroidism, which disappears often with removal of a portion of the overactive thyroid gland. Fourth, is the very interesting condition, paroxysmal hypertension, that has come to the notice both of pathologists and of clinicians within the last few years. In the present study, the term "paroxysmal hypertension" is limited to those cases in which the hypertension appeared periodically and in which tumors were found in the region of the suprarenal gland. Fifth is the hypertension that is associated with eclampsia, or, as some like to call it, the acute glomerulonephritis of pregnancy. Then comes the subdivided group which Allbutt particularly stressed, essential hypertension. For want of better terms, the subsidiary types of essential hypertension are called benign, severely benign or early malignant, and malignant.

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A boy whom we had as a patient, had definite hypertension, with a systolic blood pressure of 185 millimeters of mercury, and a diastolic pressure of 80. He had an arteriovenous aneurysm which involved the femoral artery and femoral vein. When the abnormal connection between artery and vein was excised the blood pressure returned to normal.

Another patient, a man, had congenital stenosis of the isthmus of the aorta. He entered the hospital with a diagnosis of chronic glomerulonephritis. It was interesting to note the large superficial arteries between his scapulas. Woltman and Shelden, who have been much interested in such cases for many years, were of the opinion that the main condition was the stenosis of the aorta. At one time the patient had distinct hypertension with a systolic blood pressure of 205 and a diastolic pressure of 120.

In a case of exophthalmic goiter the basal metabolic rate was +80. Use of iodine and subsequent removal of a portion of the gland caused return of the basal metabolic rate and blood pressure to normal. One of the striking features of hypertension with hyperthyroidism is the marked increase in the pulse pressure.

The first case of paroxysmal hypertension that was thoroughly described was reported by Labbé in 1922. The patient was a young woman who had crises associated with marked hypertension. At necropsy a tumor was found which apparently arose from the suprarenal gland and it was felt had a causal relationship to the attacks of severe hypertension. Since the time of Labbé's report several cases have

been noted in this country<sup>9</sup>. In three such cases a tumor was suspected, operation was advised and was carried out, and the tumor was removed. Apparent recovery and disappearance of the hypertension supervened.

One of these three cases, reported by C. H. Mayo occurred in a woman, a music teacher, of thirty years of age. One of us (Keith) saw this patient. The attacks of paroxysmal hypertension lasted from a half hour to three hours. They were very severe, and if they had continued to occur indefinitely the termination would have been fatal. After removal of a suprarenal tumor, which was reported to be a malignant blastoma, the blood pressure became and remained normal.

In the second case, reported by Pincoffs, the tumor was composed of chromophil tissue simulating that from the medulla of the suprarenal gland. In the third case, in which one of us (Keith) saw the patient before operation, the tumor was removed by Porter. The tumor apparently arose from the cortex and not from the medulla.

Wagener has described arteriolar spasm in the retina in eclampsia or acute glomerulonephritis of pregnancy, and has pointed out its importance. In this condition, vascular phenomena are associated with hypertension. This condition is illustrated by the case of a woman twenty-six years of age, in her first pregnancy, with a blood pressure as high as 180 systolic and 105 diastolic. After delivery the blood pressure dropped to normal and remained so, and three and a half years later a normal pregnancy occurred without any rise in blood pressure. In eclampsia, then there is a condition of acute

hypertension, and some of the changes that have been noted in the retinal arteries indicate that the condition which begins in the course of eclampsia possibly progresses from the acute to the chronic type.

In one case there was marked hypertension and marked toxemia of pregnancy, associated with very marked retinitis. Subsequently chronic vascular disease developed. The vascular condition may have been present before pregnancy, but after it became severe the blood pressure remained high and the condition in the arteries gradually became more marked. The patient died of cerebral hemorrhage, but at the time of postmortem examination any very definite renal injury was not found. This goes to show that in a certain group of cases of eclampsia in which the vascular condition progresses the residual lesion may be vascular rather than renal.

A number of cases of essential hypertension have been studied. One woman, for instance, has been watched for several years. In 1917 she had a very high blood pressure, 240 systolic, and 135 diastolic. Her blood pressure has remained practically the same since then. We have seen her within the last few months, but we have not seen actual retinitis. The cardiac and renal functions have remained good. This case, therefore, is of the benign type.

In the group of cases of essential hypertension, the benign type is much the commonest. It is a hopeful aspect in these cases, that there is a benign type and that it is much more frequent than the malignant type.

In 1920 a woman, aged thirty-nine years, went to the oculist for glasses

and her ocular fundi were reported to be normal. Two years later she had marked hypertension. We have been able to follow this case closely since 1922. Retinitis began to develop in 1926 and periodically, particularly within the last few weeks, it has been marked. The changes are not those seen in malignant hypertension. Nevertheless the patient has high blood pressure, diffuse vascular disease, and recurrent retinal lesions. To our way of thinking these features indicate that the condition is more severe than that in a case of benign hypertension. This patient's condition is classified as severe benign or early malignant hypertension.

In a case of malignant hypertension which finally came to necropsy, in addition to the high blood pressure there were evidences of myocardial injury. There was no evidence of severe renal injury, and yet the retinitis was typical of malignant hypertension. The patient died of a cerebral hemorrhage. There was marked thickening of the arterioles in many organs, including the kidney, and yet the glomeruli and the tubules appeared to be in splendid condition. This case, then, is one of malignant hypertension.

In eighty-one cases of malignant hypertension which we have studied thoroughly, it is evident that the condition is not a disease of old age; it is a disease of youth and middle age. We have had patients as young as eight years of age but the great majority are aged between thirty and fifty years.

In one of our malignant cases which came to necropsy the arteriolar lesions in the kidney were marked. There

were similar marked changes in the wall of an artery which was seen in a section of skeletal muscle. Changes were found in arteries of the retina, the brain, the meninges, and in the coronary artery. That is, there were diffuse pathologic changes in the arterioles. The lesions of malignant hypertension that one of us (Kernohan)<sup>5,6</sup> has stressed are hypertrophy in the media, and in some cases also intimal thickening. The finding of these changes in the intima and media led us to see if we could not get some idea as to the condition of the arterioles in the living patient. Therefore, we have now carried out biopsy of the pectoral muscle in some 100 cases. Definite decrease in the lumen has been noted, in addition to the changes in the wall in a number of these cases. In a normal small artery or arteriole the ratio of lumen to width of the wall is about two to one. In a case of longstanding benign hypertension with general arteriosclerosis there is likely to be some thickening of the walls of arterioles. It may not be marked, and the ratio of wall to lumen, in our series, averaged 1 to 1.6. In a small artery from one of our cases of severe benign hypertension there was more thickening and some increase in the number of intimal cells. In this the ratio of wall to lumen was 1 to 1.4.

There is variation in this change of

the ratio of the lumen to the thickness of the wall. In normal persons it varies from 1 to 1.5 or 2.5, averaging about 1 to 2. In benign cases the ratio averages 1 to 1.4. In our malignant, and in our severe benign or early malignant cases the ratio often approached 1 to 1.

In summing up, it behooves us as clinicians always to consider the diagnosis of a case of hypertension from the standpoint of the fundamental pathologic change. There are certain rare anatomic changes in the vascular system which give rise to hypertension, such as arteriovenous aneurysm and congenital stenosis of the isthmus of the aorta. In addition to the kidney we must think of other organs in the body as possibly being associated with the cause of hypertension. For instance, we must think of the thyroid gland and of the suprarenal gland together with tumors in the region of the latter. Also, we must think of the sympathetic nervous system, for vasoconstriction sometimes occurs in early cases of hypertension. Cases have actually been seen in which the condition has begun with vasoconstriction and in which, later, arteriolar thickening has appeared. Finally we must seek substances which will be effective in prevention of this vasoconstriction, or in its treatment when once it has developed.

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# Retinal Vascular Changes in Hypertension\*

By HENRY P. WAGENER, M.D., *Section on Ophthalmology,  
The Mayo Clinic, Rochester, Minnesota*

**A**MERE catalogue of the changes observed in the retina of patients with hypertension offers little of interest to the internist. The presence of arteriosclerosis or of arteriolosclerosis and its complications, and of retinitis, is universally recognized. From the standpoints of differential diagnosis and prognosis, retinal changes are of definite value. But the most alluring possibilities offered by the retina seem to me to lie in the field of interpretation of the basic pathologic and the pathologicophysiologic changes concerned in the production of hypertensive disease, or, at least, of some of its more serious manifestations

In my opinion, all of the branches of the central artery usually studied with the ophthalmoscope are arterioles. Visible sclerosis of these vessels, not secondary to primary disease of the optic nerve, of the retina, or of the choroid coat, is practically always evidence of hypertensive disease, whether or not the readings of blood pressure are high at the time of examination. The recognition of this fact is of importance, especially in the differential diagnosis of the types of myocardial

degeneration, as has been pointed out by O'Hare and Walker, and by Yater and Wagener. In spite of some variations in the results of statistical studies, I believe that a majority of patients with hypertension of the essential type have some sclerosis of the retinal arterioles, although this sclerosis may be minimal. If the changes in the retina are confined to mild narrowing of the caliber of the arteries, or to mild arteriosclerosis, and if these changes do not increase in severity after observation for a reasonable length of time, the hypertension ordinarily may be assumed to be benign. In the more severe forms of hypertension, sclerosis is practically always present and progressively increases in grade. Advancing sclerosis of the retinal arteries, in my opinion, always implies potentially dangerous hypertension, whether or not the sclerosis is complicated by episodes of retinitis. Even senile persons, with benign hypertension of low grade, have slight, but unmistakable, evidences of hypertension and sclerosis in the retinal arteries. In other varieties of hypertension, such as that accompanying exophthalmic goiter and coarctation of the aorta, retinal arteriosclerosis is rarely seen; nor is it found in association with glomerulonephritis unless or

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until the nephritis is complicated by the development of a diffuse vascular lesion. It has been demonstrated clearly that sclerosis of the retinal arterioles, not secondary to local disease, is part of a similar degree of sclerosis of the arterioles throughout the body. Hence, in a case of hypertension, the presence of such sclerosis of the retinal arterioles, even if it is associated with retinitis, means that this hypertension is the result, or is a symptom of, a diffuse vascular lesion and is not secondary to primary glomerulonephritis.

In the literature numerous classifications have been given of the types of retinal vascular lesions and retinitis seen in association with hypertension. It is almost universally admitted now that the occurrence of retinitis in cases of hypertension does not necessarily imply renal involvement. If exception is made of the possible relation of eclampsia to nephritis, the various forms of retinitis observed in cases of glomerulonephritis do not enter directly into this consideration. Exclusive of these, the retinitis which occurs in hypertension may be divided satisfactorily into those dependent on local vascular disease and those originating in, or at least associated with, vasoconstriction, the angiospastic retinitis of Volhard. To the first group belong isolated hemorrhages in the retina, thrombosis of individual retinal veins with resultant hemorrhage, edema and exudation into the retina, and the retinitis of arteriosclerosis. Essentially, these are all strictly localized lesions and their diagnostic and prognostic significance does not differ greatly

from that of the associated and usually causative arteriosclerosis. The observation of the course of venous thrombosis in the retina affords an opportunity for the study of the processes of vascular repair. Noting the rapidity and completeness of the compensation for the thrombosis through the formation of anastomotic circulation may perhaps afford a clue to the flexibility of the general vascular system. As a rule the healing is slower and less complete in older patients, but the degree of the associated arteriosclerosis also seems to be a factor in determining the outcome. The retinitis of arteriosclerosis is observed only in the presence of rather severe arteriosclerosis. Such patients are apparently especially subject to cerebrovascular accidents.

These localized types of retinitis should be carefully distinguished from those more generalized or diffuse types of involvement of the retina dependent on arterial constriction. The latter types of involvement always indicate progressive hypertension, and the rapidity or severity of the progression seems to be aligned with the degree and the generalization of the vasoconstriction as indicated in the retina by the extent and distribution of edema, hemorrhage, and exudation. The severity of the associated arteriosclerosis has no bearing in evaluating the prognostic significance of this retinitis, although it may afford a clue to the previous duration of the hypertension. It is possible to distinguish two distinct forms of this retinitis: one is associated with relatively benign hypertension, and the other with the ma-

lignant hypertension of Keith, Wagener, and Kernohan.

The predominant and the most interesting vascular feature of the retinal picture in the severe and rapidly progressive forms of hypertension unquestionably is arterial constriction. It is striking in the severe type of retinitis, but it is more readily studied when it is seen before the onset of retinitis. In any case in which hypertension is rapidly rising, it is the first visible change in the retinal vessels and it is definitely spastic in nature. As Haselhorst and Mylius have pointed out, the best opportunity for the study of this angiospastic process is afforded by cases of hypertension in toxemia of pregnancy. The first response visible in the retinal arteries in such cases is generalized narrowing of the blood stream. This is followed by more advanced narrowing of the arteries in localized spots or in individual branches. That these segments of advanced narrowing are produced by spasms is made evident by their shifting in situation and in degree. If the rise of blood pressure continues, the areas of constriction gradually become more extensive and more persistent in situation and duration and may be almost oblitative. From a comparative study of the retinal arteries and the capillaries of the nailfold, Haselhorst and Mylius expressed the belief that, when these spasms become definitely localized in a given situation, and are of sufficient duration and severity to produce stasis in the capillaries, edema and hemorrhage, that is, retinitis appears in the retina. At first, this retinitis is localized to the

areas of most intense spasm; later, it becomes diffuse. This has been unquestionably the sequence of events in a number of cases of toxemia of pregnancy which have been closely followed. In the cases reported by Haselhorst and Mylius, the onset of eclamptic convulsions coincided in time with the appearance of maximal constriction of the retinal arteries.

In the retinas of these pregnant women, the amount of arteriosclerosis persistent after recovery from the acute toxemia seems to be definitely proportional to the persistence of the spastic constriction and to the resultant interference, through capillary stasis, with the nutrition of the walls of the vessel and of the retina. It has been my observation that the residual injury to the general vascular system in these patients is comparable to that found in the retina although that in the general system may be less in grade if severe retinitis has increased the local retinal arteriosclerosis through secondary changes. In any event, the majority of those who have definite residual sclerosis of the retinal arteries have persistent and usually progressive diffuse vascular disease.

In a few cases of an apparently essential type of hypertension, seen soon after the onset of what might be termed the acute phase of the hypertension, changes have been observed in the retinal arteries similar to the varying spasms seen in toxemia of pregnancy. Occasionally, these have been accompanied by scattered hemorrhages and mild edema of the retina. In cases of hypertension of longer standing, and with definitely visible

sclerosis of the retinal arteries, localized spasms are more difficult to demonstrate. In such cases, however, there are frequently seen scattered areas of retinitis, similar to those seen in the early stages of the retinitis of toxemia of pregnancy, and which may be assumed perhaps to be due to the same factors. This is the type of retinitis which I term the retinitis of severe benign hypertension. It is characterized by the addition to arteriosclerosis of scattered hemorrhages and white patches, pictorially described as cotton-wool exudates. Any striking vasoconstriction and any definitely visible edema of the retina are usually confined to the region of these hemorrhages or exudates. Such retinitis may appear in slight degree and transiently in relatively benign hypertension, but as a rule it is subject to periodic appearance or to recurrence, and the hypertension associated with it, must be regarded as relatively dangerous, although it is usually amenable to control, as is the retinitis itself.

The second type, the retinitis of malignant hypertension, is quite different. In this there is usually, and always in the early stages, distinct and generalized spastic constriction of the retinal arteries, in association with generalized edema of the retina, hemorrhages, cotton-wool patches and, particularly, hyperemia and measurable edema of the disk which may reach the height of 5 to 6 diopters. The macular stars featured in many descriptions of retinitis are merely later phases of edema of the retina and are not of diagnostic significance. The cause of the edema of the disk is

not known, although it may be partially dependent on the increased pressure of the spinal fluid and the presumably increased intracranial pressure present in the majority of these cases. The outcome in cases of the typical retinitis of malignant hypertension is almost invariably fatal within a relatively short time, as Keith, Wagener and Kernohan have pointed out; very few of the patients live more than from eighteen months to two years. The retinitis usually persists in spite of treatment and the hypertension itself does not yield satisfactorily to any measures for its control.

As is to be expected, there are apparently some cases of rapidly progressive hypertension in which this typical retinitis is not seen. This is particularly true of patients who present themselves first with severe cardiac decompensation, in whom, perhaps, the capability of intense vasoconstriction is absent. In such patients, the retina gives evidence only of arteriosclerosis or at most of retinitis of a severe benign type. There are other patients who may belong in the group of malignant hypertension, whose retinitis is essentially of the severe benign type except that there is mild, diffuse edema of the retina sufficient to cause some blurring of the margins of the disk but without any definite swelling of the disk itself. There is some evidence to show that persistently recurring retinitis, of the severe benign type, may ultimately assume this form. Such patients I have tentatively placed in a borderline malignant or intermediate group. The exact prognostic significance of this type of



retinitis has not as yet been definitely determined. In a few cases, typical retinitis of malignant hypertension has resolved more or less completely and has shown no tendency to recur. Although a few of these patients have done well for a considerable period, as a rule the disease progresses to its usual rapidly fatal outcome in spite of the healing of the retinitis. Hence the fact that in certain cases the retinitis may be observed for the first time in its healed or residual stage does not alter the severity of its prognostic significance.

If it can be assumed, then, as seems justified by the histologic studies of

Keith, Wagener and Kernohan, that the same processes observed in the retina are going on in the arterioles throughout the body, it must be admitted that arterial constriction or spasm is the most dangerous element of hypertensive disease, that it may be the primary factor that results in arteriosclerosis, and that it is largely responsible, if not for the hypertension itself, at least for the retinal, cerebral and renal complications. It would seem that efforts should be directed especially to the discovery of the cause and to the relief of this tendency to arterial, or rather to arteriolar constriction.

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# The Causes of Hypertension\*†

By E. T. BELL, M. D., AND A. H. PEDERSEN, M. D., *Minneapolis, Minnesota*

**T**HIS paper deals with the various factors that regulate or influence blood pressure in health and disease. By a study of known processes we may approach the problem of primary hypertension.

## A. MECHANISMS CONCERNED IN THE REGULATION OF THE BLOOD PRESSURE

1. *The heart* The energy required to maintain or elevate the systemic blood pressure is furnished by the contraction of the left ventricle. When the peripheral resistance is increased the blood pressure must be raised, if the tissues are to receive as much blood as they did before the increase of resistance occurred. When the tissues require more blood, as during violent exercise, an increase of blood pressure is needed to force the blood through the vessels more rapidly. The heart raises the blood pressure by stronger or more frequent contractions. A compensatory hypertrophy of the left ventricle occurs when the functional demand upon the heart persists for some time.

A strong myocardium is necessary

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†From the Department of Pathology, University of Minnesota, Minneapolis.

for the maintenance of a high blood pressure. When the nutrition of the muscle is lowered by disease of the coronary arteries or general malnutrition, the heart may be unable to keep the blood pressure at a high level, even though peripheral resistance is increased. A large heart that has maintained a high blood pressure for years may finally become exhausted and allow the pressure to become subnormal.

The heart suffers more than any other organ from the effects of hypertension since it is exhausted by overwork; but hypertension is not a primary disease of the heart. The blood pressure is not elevated unless the resistance in the arterial system is increased. There is no increased output of the heart in hypertension.

2. *The small arteries and arterioles* The peripheral resistance depends upon the degree of contraction of these vessels. Their tonicity is regulated by the vasomotor center through the vasomotor nerves. When the vasomotor center is disconnected, as by section of the cervical spinal cord, there is a generalized dilation of small arteries and arterioles and a marked decrease of blood pressure. When the vasomotor nerves to any particular organ, e.g., the ear of the rabbit, are

sectioned the blood vessels dilate immediately and the organ remains congested for weeks or months, but the vessels finally regain their tone. Stimulation of the vasomotor center causes a generalized contraction of small arteries and arterioles and a rise of blood pressure.

A generalized contraction of the arterioles is necessary to increase the peripheral resistance. When the vessels of one organ only are constricted a slight relaxation elsewhere will prevent an increase of resistance.

Even in the most extreme cases of arteriosclerosis only a relatively small percentage of the arterioles show organic changes. The arterioles of the skeletal muscle, skin, bones, heart, lungs, and intestinal tract seldom show any microscopic evidence of disease. It follows then that spastic rather than organic constriction of the arterioles is the chief cause of increased peripheral resistance.

But organic disease of the arterioles of a single organ may cause hypertension indirectly through a reflex mechanism. Evidence will be presented in subsequent paragraphs to show that obstruction of arterioles in the brain and in the kidneys causes a rise of blood pressure.

3 *The capillaries.* In occasional instances the condition of the capillaries influences blood pressure. In certain forms of shock there is a widespread capillary dilation. The greater part of the circulating blood collects in the distended capillaries, and the arterial pressure consequently falls to a very low level. This type of shock occurs particularly when there is op-

portunity for the absorption of toxic substances from large masses of necrotic tissue, e.g., in infarction of the intestine. It is believed that the capillary paralysis is due to histamine poisoning, since a similar condition may be produced experimentally by injections of histamine.

There is no known disease of the capillaries which causes an increase of blood pressure.

4 *The vasomotor center.* This center regulates the tone of the small arteries and arterioles and in this way controls the blood pressure. It is influenced by stimuli of various kinds. Increased intracranial pressure causes rise of blood pressure, probably through anemia of the vasomotor center. Stimulation of sensory nerves, such as occurs in severe pain (gastric crisis of tabes, lead colic, acute cholecystitis, etc.) causes a sharp rise of blood pressure. Emotional disturbances (fear, anger, worry, etc.) may cause a rise of blood pressure. Stimulation of the central end of the depressor nerve causes a decrease of blood pressure. It is possible that substances in the circulating blood affect the vasomotor center, but none such are definitely known. Continuous stimulation of the vasomotor center probably occurs in nearly all forms of secondary hypertension and may be present in the primary form.

5 *The vasomotor nerves.* These nerves transmit impulses from the vasomotor center through the sympathetic ganglia to the muscle fibers of the blood vessels. The arteries relax when their vasomotor nerves are severed. Adrenalin stimulates the termi-

nations of the nerve fibers in the smooth muscle of blood vessels, causing spasm of the arterioles and a rise of blood pressure. Hyperirritability of the sympathetic nervous system is regarded by Kylin as the basic cause of primary hypertension. The only evidence in support of this hypothesis is obtained from a study of Raynaud's disease. In this condition there is a spastic contraction of the arteries of the lower extremities which is relieved by lumbar sympathetic ganglionectomy. Inasmuch as the blood vessels show no organic disease, the condition may well be regarded as due to overstimulation of the sympathetics. However, there is no hypertension in Raynaud's disease, the vascular spasm being restricted to relatively small areas of the body.

6 *The depressor nerves* These nerves are branches of the vagi that supply the ascending arch of the aorta. Stimulation of the central end of the sectioned nerve causes a fall of blood pressure. It is believed that an increase of blood pressure in the aorta stretches the wall of the vessel, thereby stimulating the depressor nerves. Hering and his associates have shown that complete removal of the depressor nerves in the rabbit is followed by a persistent elevation of blood pressure.

7 *The adrenals* There are three lines of evidence which indicate that the adrenals are concerned in the regulation of blood pressure. (a) It is well known that extracts of the medulla cause a sharp temporary rise of blood pressure when injected subcutaneously or intravenously. (b) In Addison's disease in which the

adrenal tissue is largely destroyed by tuberculosis or simple atrophy, the blood pressure is usually subnormal. However the blood pressure is sometimes normal and rarely there is a definite hypertension. (c) Certain malignant tumors of the adrenals are characterized by paroxysmal hypertension, and one case is reported (Vaquez, Donzelot, and Géraudel) in which the intermittent paroxysmal hypertension finally passed over into a continuous hypertension.

On the basis of these facts many investigators have suggested that primary hypertension is caused by overfunction of the adrenals. But biochemical researches do not support this view, and there are no evidences of hyperplasia of the adrenals in primary hypertension.

## B EXPERIMENTAL HYPERTENSION

1 *Injection of various pressor substances causes a transitory hypertension* The best known of these are adrenalin, pituitrin, ephedrin, and methyl guanidin. The hypertension produced is of short duration, and repeated injections do not result in chronic hypertension.

2 *Increased intracranial pressure.* In Cushing's classic experiment a cannula was inserted into the subdural space through a watertight opening in the skull and connected with a beaker of normal salt solution. The intracranial pressure was varied by raising and lowering the beaker. The intracranial pressure and the blood pressure were recorded simultaneously by mercury manometers. When the intracranial pressure was raised above

the level of the blood pressure a sharp rise of the latter occurred.\* This reaction did not take place after sectioning of the cervical spinal cord. Cushing considered the rise of blood pressure due to anemia of the vaso-motor center.

3 *Removal of the depressor nerves.* Koch and Mies produced chronic hypertension in rabbits by complete removal of the depressor nerves. In cases of long standing, arteriosclerosis of the aorta of the adrenalin type results. Hering believes that the function of the depressor nerves is to inhibit the secretion of adrenalin, and that the rise of blood pressure is due to increased secretion of adrenalin.

#### 4 *Experimental renal lesions*

(a) *Urinary obstruction.* In one of our experiments a male rabbit developed acute obstruction of the urethra following repeated catheterization. The blood pressure rose about 40 mm Hg 24 hours later. A similar hypertension was obtained in another rabbit by ligature of the penis.

\*See McGRIGOR, L., Arch. Path., 1928, V, 657, Fig. 9.

(b) *Röntgen ray atrophy.* Hartmann produced marked atrophy of both kidneys in dogs by radiating the kidneys. The animals developed hypertension and uremia.

(c) Pedersen produced severe chronic passive congestion of one kidney in rabbits in the following manner. The left renal vein is carefully dissected out and surrounded by a heavy aluminum wire. The wire is then compressed about the vein until only a small lumen is left. Care is used not to occlude the vein completely. The kidney immediately becomes swollen and cyanotic. If the constriction of the vein is too great a hemorrhagic infarct develops and the experiment fails. The kidney is removed from its bed and then covered completely with a thin membrane which is drawn snugly about the hilus (Fig. 1). It is then replaced and secured by sutures. The membrane prevents the development of collateral circulation. If the kidney is not put inside a membrane, a collateral venous circulation develops rapidly and the passive congestion disappears within a few days.

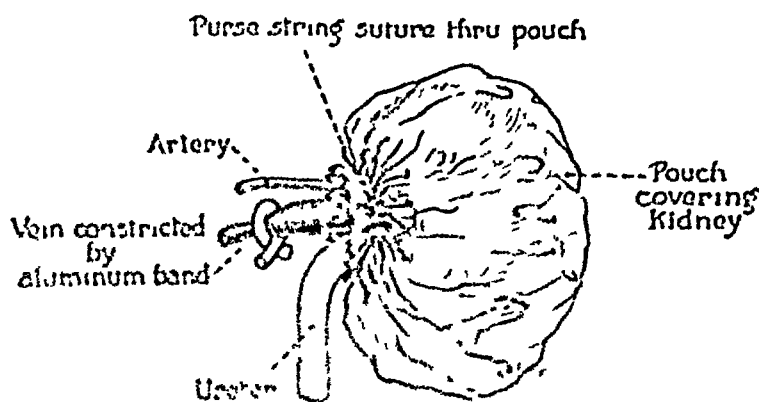


FIG. 1. Diagram illustrating a method of producing permanent venous congestion in the kidney.

By this procedure the kidney is kept distended, its capsule is tense, and the resistance to the flow of blood through it is greatly increased by the venous obstruction. After the operation the blood pressure rises slowly and remains well above the normal level for about two months, after which time it returns slowly to normal (Fig 2)

such as occurs in renal diseases in man

### C Secondary Hypertension in man

Hypertension is called secondary when it is caused by some known condition or disease. The different forms of secondary hypertension will now be described

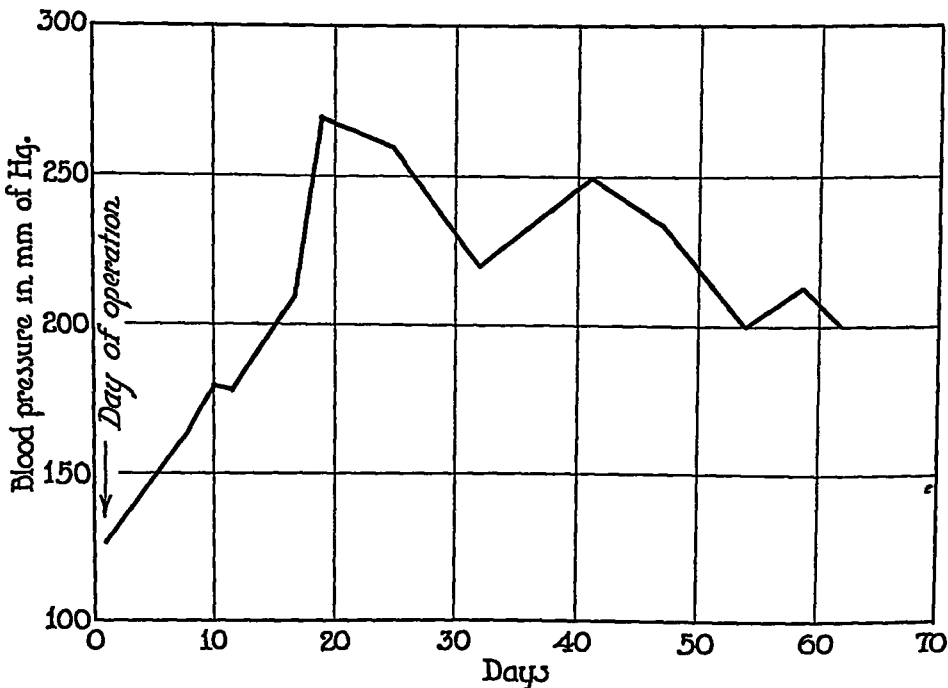


FIG 2 Graph showing the effect of permanent venous congestion of one kidney upon the systolic blood pressure

The kidney inside the membrane shows very striking changes. At the end of two months the capsule of the kidney has become enormously thickened and the parenchyma has undergone marked atrophy (Fig 3). The capsular thickening is caused by the irritation of the surrounding membrane. The atrophy of the parenchyma is due largely to the extreme passive congestion.

The hypertension is presumably due to obstruction in the renal circulation

**I Hypertension due to physical exertion** The normal individual responds to undue physical exertion with a moderate rise of systolic and a slight fall of diastolic pressure. After a short rest the blood pressure returns to normal. The decrease of the diastolic pressure corresponds with a relaxation of the peripheral vessels. Both the systolic rise and the diastolic fall of pressure serve the purpose of bringing more blood to the tissues, particularly to the active muscles.

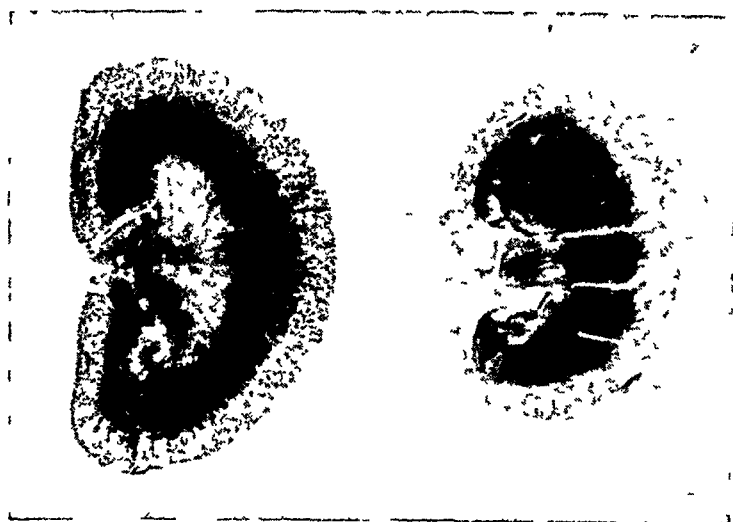


FIG. 3 a, normal kidney of rabbit, b, kidney after two months of venous congestion. Note thickening of capsule and atrophy of parenchyma.

An individual with chronic hypertension responds more readily than the normal person to physical exertion. The systolic pressure rises but the diastolic does not fall. Dyspnea develops more quickly and a much longer time is required for the blood pressure to return to its previous level (May, H).

*2 Hypertension due to sensory stimulation* Intense pain such as lead colic, the gastric crisis of tabes, acute cholecystitis, etc., often causes a marked elevation of blood pressure which persists until the pain subsides.

In the same category belongs the hypertension of emotional disturbances (fear, anger, anxiety, etc). The elevated blood pressure persists only a short time. A person with chronic hypertension responds more readily to these stimuli than the normal, and some investigators believe that a hypersusceptibility to sensory stimulation is the basis of primary hypertension.

*3. Hypertension due to increased intracranial pressure* Cushing's experiment has been described. In the usual case of apoplexy there is a mass-

ive local hemorrhage, but no uniform increase of intracranial pressure and no increased pressure on the medulla. This form of hemorrhage does not cause an increase of blood pressure, but when the blood spreads uniformly over the surface of the brain so as to compress the medulla the blood pressure increases. The majority of brain tumors do not cause a uniform increase of intracranial pressure and therefore do not cause hypertension. In an occasional case of primary hypertension the cerebrospinal fluid is under increased pressure, and a marked fall of blood pressure and improvement of symptoms follows spinal puncture.

*4. Hypertension due to adrenal tumors* This topic has been discussed in a previous paragraph.

*5 Hypertension due to renal disease* Secondary hypertension is found more frequently in association with diseases of the kidneys than with those of all other organs combined. It is evidently due to some change within the kidneys and not to the suppression

of renal function, since removal of both kidneys does not cause hypertension. Not all renal diseases result in hypertension. In general hypertension occurs in those in which there is obstruction to the blood flow, due to narrowing of the small arteries, arterioles, or glomerular capillaries.

The nephroses due to bacterial toxins do not cause hypertension. In these the renal injury is usually slight. Severe renal injury is found only in the terminal stages of infections when the circulatory system may be unable to react. The only chemical nephrosis in which hypertension has been reported is bichloride poisoning. Hypertension has never been reported in pyelonephritis or renal tuberculosis.

(a) *Glomerulonephritis.* Hypertension occurs in a large majority of instances of this disease. In mild acute cases it is not pronounced and may not be found if the patient is first examined several days after the onset. In mild chronic cases hypertension is often slight and may be absent. When the blood pressure is normal in glomerulonephritis it is usually safe to assume that the lesion is not severe. The important lesion in glomerulonephritis is swelling of the endothelium with narrowing and occlusion of the glomerular capillaries. In long standing cases the arterioles are also sclerosed and narrowed. There is obviously greatly increased resistance to the flow of blood through the kidneys.

(b) *The nephrosis of eclampsia.* Some of the toxemias of late pregnancy develop on the basis of a pre-existing glomerulonephritis. These are called nephritic toxemia. The ma-

jority, however, develop in women who had no renal disease even during early pregnancy. These latter, which may be called simple toxemia, are characterized by high blood pressure, albuminuria, and edema. In fatal cases the kidneys are enlarged, very cloudy, and fatty. In four out of eight cases which we have examined there was a marked swelling of the glomerular endothelium with narrowing of the capillaries, i.e., an acute glomerulonephritis. In the other four cases no glomerular lesions have been demonstrated. All eight cases had hypertension.

(c) *Mercuric chloride nephrosis.* In this disease hypertension has been noted frequently during the final stage of anuria. There is extensive degeneration and necrosis of the tubules. The glomeruli show severe degenerative changes but no necrosis. It is probable that the blood flow through the glomeruli is impeded by the degenerating cells, but there is no definite proof of this.

(d) *Polycystic kidneys.* The available literature indicates that about one-half of the advanced cases of polycystic kidneys in adults have hypertension. There is presumably obstruction in the renal circulation in these kidneys, but it has not been determined whether there are any structural differences between those with hypertension and those with normal blood pressure.

(e) *Urinary obstruction.* Von Monakow reports a rise of blood pressure to 170 mm Hg due to an ureteral calculus. The blood pressure fell to 112 mm Hg after removal of the stone.



Braasch reports three cases of carcinoma of the uterus that had infiltrated the broad ligaments and compressed the ureters. The blood pressure would rise during the periods of anuria but would fall to normal when the obstruction was relieved. There are numerous reports dealing with the acute hypertension that follows urinary retention due to prostatic hypertrophy. The blood pressure falls sharply after the bladder is drained.

In urinary obstruction the urine is secreted against a high intrapelvic pressure. The rise of blood pressure aids in the filtration of fluid through the glomerular capillaries.

(f) *Advanced amyloid disease of the kidneys*. Hypertension is not found in amyloid disease except in some of the cases that progress to uremia. The blood pressure is not dependent upon the size of the kidneys. The difference, if any exists, between hypertensive and nonhypertensive types has not been determined.

(g) *Sclerosis of small renal arteries and arterioles*. There is a sharp difference of opinion among investigators as to whether sclerosis of the renal vessels is a cause or an effect of hypertension. The arguments in favor of the view that the vascular disease comes first are as follows: (1) In the great majority of chronic cases in which the cause is known (secondary type) hypertension is associated with disease of the kidneys. (2) In fulminating cases of primary hypertension there is necrosis of arterioles and inflammatory changes in the glomeruli—processes which cannot be explained as a result of increased in-

travascular pressure. We cannot avoid the conclusion in cases of this type that the arteriolar and glomerular lesions are caused by some toxic substance and not by the increased blood pressure. (3) Small areas of hyaline degeneration are often seen in the renal arterioles in acute glomerulonephritis. Since the hypertension is of short duration and moderate intensity in this disease, it is more reasonable to interpret these as the effect of a toxin.

The chief argument in support of the view that hypertension is not caused by arteriosclerosis is the fact that in about ten per cent of typical clinical cases of hypertension there are no anatomic changes in the renal arterioles. These cases differ in no way clinically from those with slight or moderate arteriosclerosis, and we cannot therefore agree with Th. Fahr that the group with normal arterioles represents a different kind of hypertension. There are also many cases with only slight degeneration of the arterioles, which seem insufficient to cause much obstruction to the renal circulation unless we assume that arterioles that appear normal histologically are already rigid.

In long standing cases of chronic glomerulonephritis there is often a pronounced arteriosclerosis in the kidneys. This is interpreted by Fishberg as evidence that prolonged hypertension causes arteriosclerosis. However, it may be argued that the arteriolar degeneration is the effect of a toxin.

#### CONCLUSION

From the foregoing discussion it is evident that acute hypertension may

be caused by unusual physical exertion, stimulation of sensory nerves, emotional disturbances, increased secretion of adrenalin, increased intracranial pressure with compression of the medulla, certain chemical substances (methyl guanidin, etc.), and urinary obstruction. The stimulus causing a rise of blood pressure may act by direct or by reflex stimulation of the vasomotor center, which results in increased peripheral tonus. The stimulus may also act directly on the smooth muscle of the vessels or on the nerve terminations in the muscle. Theoretically, widespread irritation of the sympathetic ganglia or vasomotor nerves would cause hypertension, but no clinical or experimental instances of this are known.

The only clinical examples of chronic hypertension, in which the etiology is known, are those caused by disease of the kidneys. A close study of renal diseases, in which hypertension occurs, reveals lesions of three types: (a) obstruction to the flow of blood through the glomerular capillaries (glomerulonephritis, toxemia of pregnancy), (b) obstruction in the arterioles (advanced amyloid kidney, fulminating hypertension), (c) increased resistance to the excretion of fluid from the glomerular capillaries (urinary obstruction). Experimentally a fourth type of lesion causing hypertension may be added, viz., obstruction to the outflow of venous blood (experimental stenosis of the renal vein).

The proper functioning of the kidneys is necessary for life, and the rise of blood pressure is a compensatory process adapted to the preservation of

renal function under the abnormal conditions. When there is increased resistance in the renal circulation, the blood pressure must be increased in order to maintain the normal blood flow. In urinary obstruction an increase of blood pressure aids in the excretion of urine. By teleological reasoning we may conclude that afferent impulses pass from the diseased kidney to the vasomotor center and cause general vasoconstriction. However, such a reflex mechanism has not been demonstrated. Denervation of the kidneys in chronic glomerulonephritis with hypertension would determine whether such a reflex exists.

We do not know whether any of the causes of secondary hypertension are operative in the primary form, but the same mechanisms must be concerned in both types. In the early stages of primary hypertension the blood pressure falls to normal during sleep but returns to its previous level immediately upon awakening. This fact suggests that the vasomotor center is hypersensitive to sensory stimuli. In cases of long standing and especially when there is extensive renal involvement, the pressure does not fall during sleep.

A temporary fall of blood pressure is obtained with nitrites and other drugs more readily in the early stages of the disease than in the later stages, especially in those with extensive involvement of the kidneys. Either the arterioles become more rigid or the stimulation of the muscle is stronger and more constant in the later stages of the disease.

The narrowing of the arterioles over the greater part of the body is

spastic rather than organic. It is however theoretically possible that arteriosclerosis of one organ, e.g., the kidney or the brain, may cause general vascular spasm by a reflex mechanism such as apparently occurs in secondary hypertension. In acute fulminating primary hypertension it is highly probable that the arteriolar and glomerular lesions antedate and cause hypertension. We cannot explain necrosis of arterioles and glomerulitis as a result of increased blood pressure.

In cases of primary hypertension with extensive involvement of the kidneys the blood pressure is usually at a higher level and more fixed than in other types. Renal arteriosclerosis may owe its origin to hypertension, but when it has progressed to an advanced stage it has a striking effect in causing hypertension.

Renal arteriosclerosis and hypertension are associated so frequently that there must be a casual relation between them. Either one causes the other or both are the effects of some unknown cause. In the light of our present inadequate knowledge, a tenable hypothesis is the following: Hypertension begins as a spastic condition of the arterioles which in certain organs, notably the kidneys, leads to arteriosclerosis. In this way a vicious cycle is established each condition aggravating the other. In the event that an infection supervenes the renal arterioles and glomeruli may be severely damaged so that a fulminating hypertension with uræmia develops.

No adequate explanation of primary hypertension has ever been offered. It is known that inheritance is of great

importance. It is frequently observed in several members of a family. It is said to be very rare in the Chinese and in primitive African tribes. What is inherited is evidently an inferior vascular system which either reacts excessively to the environment or degenerates and becomes rigid from inherent weakness without the factor of overstimulation. It is largely a disease of advanced life. The cases that occur in young persons are usually of the renal type, and probably represent a primary renal disease.

In most instances of primary hypertension there is no adequate evidence that it begins as a renal disease. This question could probably be settled finally if some courageous surgeon would denervate the kidneys in a case of primary hypertension.

Occupation is without influence in the origin of hypertension, but excessive physical or mental strain may greatly aggravate an existing hypertension.

#### SUMMARY

The physiologic mechanisms concerned with the regulation of blood pressure in health and disease are discussed, viz., the heart, the arteries and the arterioles, the capillaries, the vasomotor center, the vasomotor nerves, the depressor nerves, and the adrenals.

Hypertension has been produced experimentally in animals by pressor substances, increased intracranial pressure, removal of the depressor nerves, urinary obstruction, roentgen-ray atrophy of the kidneys, and stenosis of the renal vein.

Secondary hypertension of acute type occurs in man from physical ex-

ertion, sensory stimuli, increased intracranial pressure, and adrenal tumours

Secondary hypertension of acute or chronic type occurs with glomerulonephritis, nephrosis of eclampsia, bichloride nephrosis, polycystic kidneys, urinary obstruction, advanced amyloid disease, and degeneration of small renal arteries and arterioles

Secondary hypertension of chronic type is seldom seen except in association with renal disease

Obstruction in the renal circulation or obstruction of the outflow of urine seems to cause hypertension, probably

through a reflex mechanism. Renal insufficiency alone does not cause a rise in blood pressure

Acute fulminating hypertension is probably a primary renal disease

Primary hypertension has its basis in inheritance. The defect inherited is an inferior vascular system which either reacts excessively to ordinary environmental stimuli or degenerates from inherent weakness

References to the literature of hypertension may be found in Bell, E. T. and Clawson, B. J. A study of 420 cases of primary hypertension. *Arch Path.*, 1928, v, 939-1002

# Undulant Fever (Brucelliasis)\*†

## A Clinicopathologic Study of Ninety Cases Occurring in and About Dayton, Ohio

By WALTER M. SIMPSON, M S, M D, F A C P, *Dayton, Ohio*

UNDULANT fever is now recognized as a common disease of man. The knowledge of its widespread distribution, particularly in this country, is largely a development of the past two years. At a recent meeting of the Health Section of the League of Nations, it was stated that undulant fever is the most important problem facing public health workers at the present time. Prior to 1925, 128 cases of undulant fever had been recorded in this country. During the period from 1925 to 1928, the recorded cases numbered 24, 46, and 217 respectively; during 1928, largely due to the dissemination of information regarding the disease, 649 cases were recorded<sup>1</sup>. The writer has conducted a nation-wide survey of the number of cases of undulant fever recorded by state health departments during 1929; this survey reveals that 1301 cases, occurring in every state of the Union, were reported during the past year. This total of 2365 cases does not include the indeterminable num-

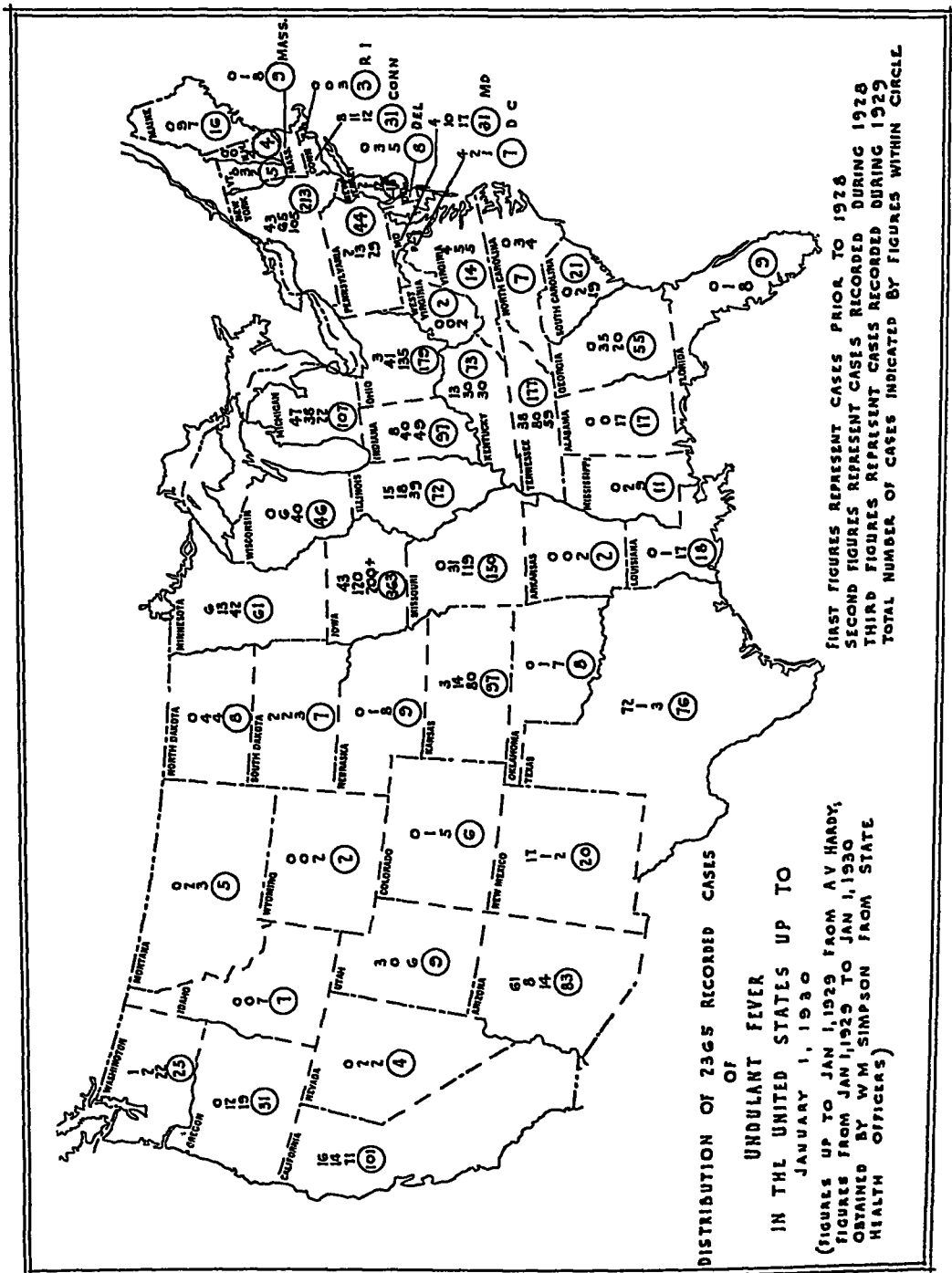
ber of cases which have been recognized as the result of confirmatory laboratory studies carried out in hospital and private laboratories, since not all state health departments list undulant fever as a reportable disease.

The writer has investigated 90 confirmed cases of undulant fever in and about Dayton, Ohio, during the past 18 months. The first 63 of these cases are reported elsewhere<sup>2</sup>. These findings were the result of a determined effort to learn of the incidence of the disease in a given locality. Hardy<sup>3</sup>, activated by a similar motive, has investigated over 300 cases in Iowa. Carpenter<sup>4</sup> in New York, Huddleson<sup>5</sup> in Michigan, King<sup>6</sup> in New York, Bierring<sup>7</sup> in Iowa, Farbar and Mathews<sup>8</sup> in Indiana, Brown<sup>9</sup> in Kansas, Sensenich and Giordano<sup>10</sup> in Indiana, and Ey<sup>11</sup> in Ohio, have conducted similar investigations in their localities, their efforts have likewise been rewarded by the discovery of a large number of cases. The inference is obvious that the disease must be much more prevalent than is generally believed.

American physicians should derive great pride from the fact that the re-awakening of international interest in this disease has been the direct result

\*From the Diagnostic Laboratories of the Miami Valley Hospital, Dayton, Ohio.

†Presented, in part, before the Fourteenth Annual Clinical Session of the American College of Physicians, New York, February 13, 1930.



of the discoveries of American workers. The leader among these is Alice C. Evans<sup>12</sup>, bacteriologist of the United States Public Health Service, who, in 1918, published the results of a comparative study of the organisms then known as *Bacillus abortus* of Bang, the cause of contagious abortion of

cattle, and *Micrococcus melitensis* of Bruce, the etiologic organism of Malta fever. Evans had discovered that the two organisms were indistinguishable morphologically, biochemically, culturally and by ordinary agglutination reactions. She found that pregnant guinea pigs inoculated with either

organism produced the same percentage of abortions Evans<sup>13</sup> also demonstrated that *Brucella melitensis* behaved exactly like *Brucella abortus* when injected into a pregnant heifer. Shortly after these discoveries, Fleischner, Veckl, Shaw and Meyer<sup>14</sup> found that *Brucella abortus* produced a disease in monkeys identical with that produced by *Brucella melitensis*. In 1927, Carpenter<sup>15</sup> recovered from the blood of 10 human beings with undulant fever an organism indistinguishable from the organism of contagious abortion; 5 pregnant heifers aborted promptly after inoculation with these cultures. For twenty years these two organisms had been regarded as separate, unrelated species. The remarkable observations of Evans have been confirmed by many workers in this country, Germany, Austria, France, England, Denmark, Italy, Netherlands, Egypt, Tunisia, and Japan.

\*In a recent communication to the author, Doctor C. W. Stiles, Secretary of the International Congress on Zoological Nomenclature has commented as follows in regard to the question as to whether the various types of *Brucella melitensis* should be considered as separate species:

"The difference between 'a species' and 'a variety' is purely subjective and this subjective difference of opinion varies not only among authors but also from time to time with one and the same author. In case of difference of opinion, two courses are possible, namely: (a) to consider two units as distinct species; this has the advantage of simplifying the nomenclature, for instance *Brucella suis* in place of *Brucella melitensis suis*, or (b) to consider two units as varieties of one species; this has the advantage of showing close relationship. Thus, to the uninitiated, *Brucella suis* might appear that this organism has only more than 20% re-

### Terminology

It became immediately apparent that a new terminology was indicated for these organisms. Meyer and Shaw<sup>16</sup> proposed that the *abortus-melitensis* group of organisms should be designated by the generic name *Brucella*, thus honoring Bruce, who discovered the Malta fever organism in 1887. Their suggestion has met with universal approval. Even though the caprine, and the so-called bovine and porcine strains of the organism are unquestionably serologic varieties of the same species, the name *Brucella melitensis* is generally used to designate the variety usually found in goats, while the name *Brucella melitensis* variety *abortus*, or *Brucella abortus*, has been applied to the variety found commonly in cows and hogs, the latter variety has been further divided by some writers into bovine (*bovis*) and porcine (*suis*) types.\* Until it has been more conclusively demonstrated that the so-

lation to *Br. melitensis* or *Br. abortus*, while *Br. melitensis suis* would indicate close relationship between *melitensis* and *suis*. This is of considerable practical importance, especially for authors who think of *Brucella* as a synonym of *Bacillus*. In the transitional stage of our knowledge of any units, experience shows that subgenera and subspecies permit a more conservative position than do genera and species, and in addition permit all of the taxonomic advantages of genera and species. The numerous synonyms *culter* and *anophlet* are cases in point.

While holding an open mind in regard to the eventual specific status of *abortus* and *suis* in the present state of our knowledge it is more conservative not only from the bacteriological and medical viewpoints, but also from the standpoint of nomenclature to retain the name *Brucella melitensis* for the goat strain as the most conservative.

called caprine, porcine and bovine strains possess unique characteristics, it might be well to refer to all of the organisms as "the *Brucella*", and to designate the disease produced by these organisms in animals and man as *Brucellosis*. The names which have been used to designate the disease in animals and man (contagious or infectious abortion, Malta fever, undulant fever) appear to be inadequate in the light of present knowledge.

### Sources of Infection

Undulant fever of goat origin is of importance in a relatively restricted area in this country, notably in Texas, Arizona and New Mexico. It is the enormous number of cases of undulant fever due to infection with the organism of contagious abortion of cattle and hogs that has arrested the attention of investigators in this country. No uniformly reliable method for distinguishing between the porcine and bovine strains has been devised.\*

\*In a recent communication with the author, Charles M. Carpenter makes the following statements:

"Although there are many statements in the literature concerning the differentiation of porcine strains of *Br. abortus* from the bovine strains, I am certain that none of them can be relied upon. For instance, the following conclusions may be found: Theobald Smith stated that the porcine strains produce abscesses in the lymph nodes and spleen of guinea pigs, while the bovine strains do not. In a recent article by Smith on a study of a porcine strain, he concludes that it is more like the bovine strain than any of the others he has examined. McAlpine and Slanetz, in studying the biological activities of this group, concluded that the porcine strains utilize glucose and are more like *melitensis* than are the bovine strains. Soule, by studying the metabolic activities of the two organisms, find that both the bovine and porcine strains utilize glucose. Miss Coleman has just reported a study of the effect of strains of *Br. abortus* on monosaccharids, and finds that the porcine strains do not ferment these carbohydrates, while the bovine strains do. She has used a different technique from that of any of the other investigators mentioned. Huddleson has reported that the growth of the porcine strains is inhibited by a one to two hundred fifty thousand dilution of gentian violet, while the bovine strains are affected only by one to fifty thousand and one to one hundred thousand. He finds that the bovine strains are more like *melitensis*. Although we have studied only a comparatively few porcine cultures of *Br. abortus* in this country, they do seem to be more pathogenic

for guinea pigs than are the majority of the bovine cultures. My opinions are expressed in a discussion at the end of the article by Carpenter and Baker in the Cornell Veterinarian for April, 1927. I do not believe that we are justified in stating that porcine strains have been recovered from cow's milk until we have a more satisfactory method of differentiating these strains. I believe that any strains isolated from cattle should be called bovine, and any cultures from swine should be called porcine, etc. I think that it is very confusing to say that bovine cultures are isolated from man, and that porcine may be isolated from a horse or a cow, etc."

Alice C. Evans commented as follows in a recent communication with the author:

"It is true that the porcine type of *Brucella* infects cattle, and that is also true of the caprine type of the organism. The porcine and bovine types are indistinguishable by the agglutination absorption test, and by other tests. There are, however, certain differences. The porcine type is more pathogenic than the bovine type (see Huddleson's recent article in the October 1929 Journal of Infectious Diseases). This difference in pathogenicity is one of degree, however, and as both types vary in degrees of pathogenicity, there is no definite dividing line to distinguish them in this respect. The bovine type is favored by a reduced oxygen tension in the first few generations after isolation—a distinguishing characteristic which is soon lost. The work of McAlpine and of Huddleson have shown that the two types differ in the virulence of the cultures and in susceptibility to dye.



There is some evidence that certain porcine strains are more pathogenic for experimental animals than the bovine variety, but many of the strains which have been designated as porcine have been recovered from cow's milk. Carpenter<sup>4</sup>, King<sup>6</sup> and Huddleson<sup>5</sup> have found that the bovine strain has been responsible for the great majority of the cases of undulant fever which they have investigated. Carpenter and King analysed 155 cases of undulant fever and found that only 7 per cent had had any possible contact with swine, no information was obtained in 22 per cent of cases, while 70 per cent were consumers of raw milk, which in the majority of cases was proved to be infected with the bovine strain of *Brucella abortus*. In the 90 cases studied by the writer, there is no evidence of direct goat or hog origin. All of our patients were consumers of raw milk or unpasteurized dairy products. Four cultures of *Brucella abortus* recovered by the writer (3 from cow's milk, 1 from human blood) were found by Huddleson to be of the bovine type. After a careful review of the indefinite evidence as to the relative pathogenicity of the bovine and porcine strains, Hardy<sup>7</sup> states: "A classification of isolated strains is important, but it seems evident that this will not be a reliable index of the importance of the different varieties as a cause of human disease."

That the great majority of human infections with *Brucella abortus* have been the result of the ingestion of the organisms is well established. As regards the dissemination of the disease

among cattle, Fitch<sup>17</sup> states that "the chief, if not the only important channel of infection, is through the digestive tract." Hardy<sup>18</sup> has recently conducted animal experiments which have demonstrated that the skin may be a portal of entry. This mode of infection assumes greatest importance in those persons whose occupations bring them in direct contact with infected fresh animal tissues. It is probable that some cases of undulant fever which have occurred in packing house workers, particularly those who "kill and cut", or in veterinarians and farmers who have handled the products of abortion with bare hands, have originated in this manner.

#### *Distribution Among Cattle*

"Contagious abortion" is an unfortunate misnomer for the disease of cattle and other domestic animals produced by the genus *Brucella*. If one relied only on a history of abortion, less than half of the *Brucella abortus* infections among cattle would be recognized. The disease frequently affects non-pregnant cows, some infected pregnant cows do not abort, the disease commonly affects bulls, calves possess a relative immunity. The disease is widespread among cattle in this country. Ninety per cent of the herds of Connecticut<sup>19</sup> and 86 per cent of the herds of Pennsylvania<sup>20</sup> are said to be infected. Hirschboeck<sup>1</sup> reports that Fenstermacher has tested 16,310 cattle at the University Farm at St. Paul during the past 6 years, of which 1038 (30 per cent) gave strongly positive serological reaction, while 924 (6 per cent) reacted positively in distribution below 1 year. One or more

tigations indicate that the disease is widespread in southern Ohio. Serological studies of 103 cattle, including 8 calves and 6 bulls, of 7 herds which supplied milk to 18 of our patients with undulant fever, revealed that 76 of the cows (86 per cent) and all 6 of the bulls were positive reactors. The serums of the 8 calves gave entirely negative results, in this regard, it is noteworthy that veterinarians have observed that the infection rarely, if ever, exists in sexually immature animals, and that the susceptibility of young cattle increases with the development of sexual maturity. Farmers' Bulletin 1536 (1927) of the United States Department of Agriculture states that "calves seem to be wholly immune against abortion bacilli." The organism exhibits a predilection for the mammary glands and endometrium of mature cows. Until these tissues have reached full development they do not appear to offer a suitable nidus for the growth of the organism. It seems probable that the same situation obtains during the pre-adolescent period in human beings.

A single sample of the milk of ten of the cows supplying milk to Dayton patients with undulant fever was found to contain *Brucella abortus* in large numbers. These organisms were serologically identical with cultures derived from the blood of 7 of our patients suffering from the acute manifestations of undulant fever.

In a high proportion of cows whose serums show the presence of anti-*abortus* agglutinins the organism can be recovered from the milk, some infected cows continue to eliminate the

organism throughout their lifetime. Schroeder and Cotton<sup>23</sup> found *Brucella abortus* in the milk of 83.5 per cent of cows whose serum showed specific agglutinins for this organism. Carpenter<sup>24</sup> has isolated *Brucella abortus* from the milk of 66 per cent of a group of cows which had either aborted or had retained placenta at least once during 3 previous gestation periods. Special emphasis should be placed on the fact that Carpenter has recovered the organism from the milk of 3 cows whose serums showed no anti-*abortus* agglutinins. King<sup>6</sup> isolated *Brucella abortus* from the milk of 2 cows in which no specific serum agglutinins were present. In the 1928 report of the Committee on Abortion of the American Veterinary Medical Association<sup>22</sup>, it was stated that "the clean herd is one in which there are no reactors to the blood test." It also states that "the agglutination test does not disclose animals in the incubative stage of the disease." This fact, together with the evidence that occasional cows that are eliminating *Brucella abortus* in their milk do not give a positive blood reaction, led this committee to state "In order to avoid the possibility of farmers securing the false impression that cattle which fail to react to the blood test will never abort, the Committee recommends dropping the terms 'abortion-free cows' and 'abortion-free herds' when speaking as well as writing about cattle abortion." King also found that 54 per cent of a high grade herd of 151 cows were infected with *Brucella abortus*, even though the milk of this herd was certified 20.2 per cent of

the infected cows were eliminating the organism in their milk. Carpenter and King<sup>4</sup> found *Brucella abortus* in 20.4 per cent of samples of raw milk supplied to 67 small towns, 2 small cities and one city of 200,000. Fleischner and Meyer<sup>25</sup>, after inoculating guinea pigs with certified milk, conclude that "*Brucella abortus* is, for all practical purposes, always present in the certified milk produced in the San Francisco Bay regions." Peters<sup>26</sup> discovered that 39 per cent of the cows supplying certified milk to Cincinnati, were positive *abortus* reactors, this discovery was followed by the passage of a city ordinance requiring the pasteurization of all milk, including certified milk.

#### *Clinical Manifestations in Man*

Because undulant fever presents many symptoms and signs common to typhoid fever, malaria, tuberculosis and influenza, it is frequently confused with these diseases. Many physicians have arrived at a tardy diagnosis of undulant fever only after repeated negative Widal reactions, the failure to demonstrate the malarial plasmodium, and the inability to elicit physical signs or roentgenographic evidence of tuberculosis. Less often, the disease has been confused with acute rheumatic fever and subacute bacterial endocarditis.

Many writers have stated that the clinical diagnosis of undulant fever entails great difficulties, and that the first thought of undulant fever usually emanates from the laboratory. Our experience does not justify such a belief. In nearly one-half of the Dayton cases the initial clinical diagnosis

has been undulant fever, and the aid of the writer was sought only to confirm the clinical diagnosis. Many of the early cases of undulant fever encountered in Dayton were demonstrated at local medical meetings. As soon as Dayton physicians became aware of the characteristics of the disease, an initial clinical diagnosis of undulant fever was made in the great majority of succeeding cases.

Hardy, Bierring and others have found that the disease occurs predominantly in the male sex. In all probability, some of the infections occurring in farming communities are the result of direct contact with infected animals. This fact has been used by some individuals as an argument against milk-borne infection. Persons who have direct contact with infected cattle and hogs on farms are almost invariably raw milk consumers. Furthermore, the male population of most farms exceeds the female. In the urban studies conducted by Hardy, Farbar and Mathews, Jones, Giordano and the writer, in which contact with livestock is practically absent, the disease occurs with almost equal frequency among men and women. In the Dayton series, the females (49) outnumbered the males (41). Urban studies likewise demonstrate that males are not more susceptible to the disease than females. The great majority of the Dayton patients with undulant fever were engaged in non-agricultural pursuits; only 14 were farmers or dairymen.

Even though children appear to possess the same relative immunity as adults, we have encountered nine *Brucella abortus* infections in children. In

tween the ages of 6 and 10. Kohlbry<sup>27</sup>, of Duluth, has recently reported the disease in a one year old infant. In our experience the disease occurs most frequently during the third and fourth decades of life. In 8 families more than one member was affected.

It is a difficult matter to determine the incubation period with accuracy, it has been found to vary from 5 to 14 days.

The prodrome is usually that of any general infection, although in 4 of our cases the disease was initiated with a sharp chill and a rapid elevation of temperature to 103-105° F. Ordinarily, the patient becomes gradually aware of an afternoon or evening rise in temperature, associated with chills, nocturnal perspiration, and marked weakness. These onset symptoms are usually accompanied by headache, and pains in the muscles, joints and extremities.

In most instances, the fever, chills and sweats follow a somewhat characteristic course. The patient usually feels quite well in the morning. As the elevation of temperature develops, usually during the afternoon and evening, the symptoms return. The nocturnal febrile exacerbations occasionally reach great heights (106-107° F). The average maximum fever in our cases was 103° F. There is often a great disparity between the subjective sense of feverishness and the extent of the fever as registered by the clinical thermometer, in many instances, the patient has neither presented a febrile appearance, nor has he complained of feverishness, but the physician has found to his great surprise

a fever of 102 to 103° F. As the fever abates, chills and sweats occur. If the defervescence is rapid, the perspiration is more apt to be of a drenching character. In 2 of our cases, the febrile exacerbations, chills and sweats occurred during the forenoon hours. In 24 cases the chills usually one a day, were of sufficient severity to be regarded as true rigors. In 8 of our patients, who experienced fever and sweats, chills were absent.

The perspiration usually occurs during the early morning hours, and in about one-half of our cases was of a drenching character. To such patients, the sweats are the most impressive feature of the disease, since the sense of weakness is pronounced during and immediately after this experience. Many physicians have noted a peculiar sweetish, fetid odor to the perspiration.

In 60 per cent of our cases the pulse rate has been disproportionately slow during the febrile episodes. In the remaining minority of cases the elevation of fever was paralleled by a proportionate increase in pulse rate. Cardiovascular symptoms are not of importance in most cases. A moderate depression of blood pressure was the usual finding. Moore and Carpenter<sup>28</sup>, Scott and Saphir<sup>29</sup> and de La Chapelle<sup>10</sup> have reported cases of subacute vegetative endocarditis associated with *Brucella abortus* bacteremia in the first 2 cases and with *Brucella melitensis* variety *melitensis* A bacteremia in the third case.

Marked restlessness and insomnia usually accompany the nocturnal febrile exacerbations. Delirium occurred in 6 of our cases in which the

fever reached great heights. Ordinarily, the mental state remains clear, the sluggish mentality described as the "typhoidal state" was not observed.

The matutinal remissions or intermissions and the nocturnal exacerbations of fever may last from one week to several months. There is indisputable evidence that the disease may persist for several years. The name "undulant fever" was given to the disease discovered in Malta because of recurring relapses and remissions of fever. Recurring febrile relapses have been the exception rather than the rule in our cases, and in those of Hardy, Bierring, and Sensenich and Giordano. Recurring undulations of fever have appeared in only 11 of our cases. In 89 per cent of cases, the patient has experienced but one febrile period, lasting from one week to several months, and finally reaching the normal level by lysis. The percentage of recurrences may be increased as these cases are studied over a longer period.

Approximately one-fourth of our patients experienced a relatively short and mild illness. Eleven patients remained at their work throughout the febrile period, more because of economic pressure than through choice. In most of these cases an original diagnosis of influenza had been made, which leads the writer to suspect that many of the milder cases of undulant fever have been frequently regarded as cases of influenza.

Anorexia was a complaint in about one-half of our patients. The outstanding feature of the gastrointes-

tinal effects of the disease was constipation, which was present in two-thirds of the cases. Amoss<sup>31</sup> has recently recovered *Brucella* organisms from the stools of 2 patients, one of whom was in the sixteenth month of his infection. There is little or no evidence of man-to-man infection by organisms eliminated in the stools. Nausea, vomiting and diarrhea were absent in our cases. The absence of diarrhea helps to distinguish the disease from typhoid fever, in which disease diarrhea occurs in about 30 per cent of cases (Osler). Meteorism, likewise common in typhoid fever, is rare in undulant fever, having been a source of complaint in but 4 cases. The tongue usually becomes coated with a yellowish fur and many physicians have been impressed by the fetid breath.

Loss of weight was an almost constant feature of the disease. The greatest loss was 62 pounds over a period of 6 weeks. Four patients lost more than 50 pounds. Thirty-four patients lost between 25 and 50 pounds. Forty-two lost less than 25 pounds. Ten patients experienced no appreciable loss in weight.

There is often a remarkable absence of positive physical findings. More than one-half of our patients did not appear to be particularly ill. Practically all presented stigmata of weakness and fatigue. The spleen was palpable in one-third of the cases. In only 4 instances was the splenomegaly marked (3 to 8 cm below the costal margin). In the remaining cases, the inferior pole of the spleen was palpable on deep inspiration at the level of the

rib margin or just above. The liver was palpable in only 4 instances. Generalized lymphadenopathy was not observed.

In 31 of our cases, tenderness or pain of the joints was noted. In 4 cases, the presence of migrating pain in the larger joints led to an initial diagnosis of acute rheumatic fever. Intermittent hydrarthrosis occurred in one case. The organism has been recovered from aspirated joint fluid. The involvement of the joints is apparently due to a transient periarthritides. No permanent impairment of the joints was observed.

Abdominal pain was a major complaint in 16 of the Dayton cases. Among 125 Iowa cases studied by Hardy, abdominal pain was present in 40 cases; in 10 instances it was the chief complaint, and was a marked feature of the disease in 24 other cases. The abdominal pain is most common early in the course of the disease. In 7 of our cases, the pain was located in the epigastrium, in 4 cases, it occurred in the right upper quadrant, while in 5 instances it was most marked in the right lower quadrant. Appendectomy was performed in 4 cases in which there was sudden development of right lower quadrant pain, accompanied by fever. In one instance, gangrenous appendicitis developed during the third week of illness, this case is reported in detail elsewhere<sup>12</sup>. In the other 3 cases, normal appendices were removed. In the latter cases, the surgeons requested the agglutination test for undulant fever after operation in their effort to determine the cause of the abdomi-

nal pain. After the agglutination test was found to be positive, a typical undulant fever history was elicited in each case. In one of our cases, cholecystectomy was contemplated because of the development of sharp upper right quadrant pain associated with fever, chills and sweats. The writer has learned of 12 appendectomies and 2 cholecystectomies which have been performed on patients with undulant fever, in which the pathological examination revealed no evidence of any active inflammatory process in the appendices or gall bladders.

There is convincing evidence that *Brucella abortus* exhibits the same selectivity for the genital tract of human beings as it does in cows and bulls. Painful swelling of the testes was a prominent feature of the disease in 16 of our cases and in 4 of Hardy's cases. Seminal vesiculitis and orchitis are common complications in the bull, there is some evidence that the disease may be transmitted to cows by the seminal route. Orchitis is a common result when guinea pigs are inoculated with the organism. Genito-urinary surgeons found evidence of seminal vesiculitis, prostatitis, epididymitis and orchitis in 3 of the Dayton patients. The history and laboratory findings eliminated gonorrhea from consideration. The serums of the 3 men agglutinated *Brucella abortus* in dilutions from 1:160 to 1:640; the organism was recovered in one case from a draining sinus tract which extended from the globus major of the epididymis through the scrotal wall. All 3 of the men were raw milk consumers. None was in direct contact with infected cattle or hogs.

The causative organism derives its name (*Brucella abortus* or the organism of contagious or infectious abortion) from its known etiologic association with abortion in cattle and other domestic animals. It naturally becomes a matter of paramount importance to determine whether or not the disease may have a similar effect on pregnant women. Several reports have appeared<sup>33</sup> describing cases of human abortion occurring on farms where the cattle were known to be affected with contagious abortion. This circumstantial evidence has been augmented by proof as the result of the isolation of *Brucella abortus* by Carpenter<sup>35</sup> from a human fetus which was aborted at the end of the fourth month of gestation. We have encountered 5 cases in which women who have repeatedly aborted, and who presented no clinical or serological evidence of syphilis, gave serological evidence of *Brucella abortus* infection: the agglutinin titers ranged from 1:80 to 1:320. Four of the five women gave histories of a previous febrile illness, entirely compatible with a clinical diagnosis of undulant fever, at intervals from 3 to 6 years previously. All were raw milk drinkers; none had had direct contact with cattle or hogs. A pure culture of the organism has been isolated from a tubo-ovarian abscess which developed as a late complication in a case of known undulant fever. These findings should be a stimulus for further investigations in cases of human abortion.

A skin eruption occurred in 10 of our cases. The lesions were generalized and took the form of small macules in all but one instance, in which

the eruption was maculo-papular. In 3 cases, the lesions were most prominent on the abdomen and simulated the roseola of typhoid fever.

The blood count and differential smear yield important information. A mild degree of secondary anemia is usually present. *Leucocytosis is uncommon*, even when the fever is quite high. Leucopenia (4,000 to 6,000) with lymphocytosis is the rule, having occurred in all but 12 of our cases. In 8 cases, the lymphocytosis exceeded 50 per cent. In only 2 cases did the leucocyte count exceed 10,000, in the remaining 10 cases, the white cell count was within normal limits.

The urinalysis usually reveals the trace of albumin commonly found in febrile diseases. The cerebrospinal fluid of 3 of our patients showed no abnormalities.

The average duration of illness in our experience was approximately 4 months. Five patients were confined to bed for less than one week. In one case, there is convincing evidence of relapses and remissions extending over a period of 8 years. While the disease is rarely fatal, undulant fever is of great economic importance because of the long period of incapacitation in the average case. Many individuals are unable to work, or are capable of performing only part-time duties for many weeks or months after the fever has subsided, because of the weakness which is a constant characteristic of the convalescence. One death occurred in our series. Various writers give the death rate as from 2 to 5 per cent.

There seems to be no doubt that many human beings possess a natural

immunity to *Brucella* infection. There is also strong evidence of a great difference in the degree of virulence of the species *Brucella*. As in many other infectious diseases, the simultaneous exposure of many persons to the same strain of organisms will produce no infection in those who possess natural or acquired immunity, but will produce a mild or severe infection in others depending upon the relative degree of susceptibility. Huddleson and Hallman<sup>36</sup> have demonstrated this difference of virulence of the *Brucella* and the difference of susceptibility to infection in *Macaculus rhesus* monkeys. The failure of certain observers to reproduce the disease in animals and man is explainable on this basis, particularly when the organisms have lost their virulence due to long cultivation in an artificial medium. To quote Evans<sup>37</sup>, "It is well recognized that pathogenic bacteria lose their virulence when grown on artificial media and this loss of virulence has been commonly noted in the organism of contagious abortion."

### Diagnosis

If undulant fever is given consideration in the differential diagnosis of all cases of febrile illness, in which the diagnostic criteria for malaria, typhoid fever, tuberculosis, influenza, rheumatic fever or bacterial endocarditis are not convincing, the disease will be recognized with much greater frequency. This is true in cases of vague, mild febrile disease as well as in those in which the clinical manifestations of undulant fever are more clearly defined. In such cases, it should become an established routine to submit

4 or 5 cc of the patient's blood, collected exactly as for the Wassermann test, to a laboratory equipped with the proper *abortus* antigen for the agglutination test. Practically all of the state health laboratories are now carrying out this simple test. It is now possible to obtain prepared *abortus* antigen from several manufacturers of biological products.

Anti*abortus* serum agglutinins may appear as early as the fifth day, but in most instances they appear sometime during the second week of illness. It is, therefore, unwise to collect the blood specimen for the agglutination test until a week or ten days after the onset of illness. In 7 of our cases, agglutinins did not appear until the third or fourth week of illness. Consequently, it is wise to submit a second and third specimen at intervals of a week in cases in which the first test has been negative.

The whole blood, without the addition of anticoagulants, or the clear serum should be sent to the laboratory. Dried blood specimens on slides are unsatisfactory for an accurate test.

We have used routinely the method adopted as standard by the Hygienic Laboratory of the United States Public Health Service in our agglutination tests. For the past year, we have used as a control the rapid macroscopic agglutination method of Huddleson<sup>38</sup>, with uniformly successful results. Using the Antigen-Huddleson (Mulford), this simple procedure is easily adaptable to office use.

We have observed the pro-agglutinoïd zone phenomenon, in which agglutination is absent in the lower di-



lutions, but present in the higher dilutions in 4 instances. It is important, therefore, that the test be carried out in all dilutions to 1:640.

The antiabortus agglutinin titer rises to variable heights during the acute manifestations of the disease and tends to fall as the fever abates. In most instances, agglutination in dilutions of 1:160 to 1:1280 will be found during the third or fourth week of illness. In one of our cases, agglutination occurred in all dilutions to 1:20,480 during the fourth week of illness. Agglutinins do not remain permanently in the serum with the same constancy that they do in tularemia. Many will retain the antiabortus agglutinins for many months or years, while in other cases they will entirely disappear a few months after recovery.

These observations should induce a measure of caution in the interpretation of positive agglutination in low titer. An individual may be suffering from some other febrile disease at the time of the test, and the simultaneous presence of antiabortus agglutinins may represent the residual titer of a previous attack of undulant fever.

Carpenter, Boak and Chapman<sup>34</sup> have submitted evidence which indicates that the presence of *Brucella abortus* agglutinins is the result of actual invasion of the tissues by living organisms; they were unable to demonstrate antiabortus agglutinins in the serums of adults who had been drinking pasteurized milk containing such antibodies.

The antigenic properties of certain strains of *Brucella abortus* vary widely. Carpenter and Evans have iso-

lated *Brucella abortus* from the blood of human beings whose serum showed no antiabortus agglutinins. Carpenter<sup>35</sup> has found that about 6 per cent of patients from whose blood he has isolated *Brucella abortus* fail to show antiabortus agglutinins in their serum. Then, too, some patients in whom the clinical picture of undulant fever is well-defined and from whose blood *Brucella abortus* has been recovered, will show agglutination in titers below 1:80. For practical purposes, most laboratorians have regarded titers of 1:80 or above as diagnostic. Evidence recently accumulated hardly justifies such an arbitrary rule. In patients in whom the clinical manifestations strongly suggest a clinical diagnosis of undulant fever, the absence of agglutinins or the presence of agglutinins in titers of 1:10 to 1:40 should lead to further bacteriological and serological studies. We have found the skin test to be of value in such cases.

The occasional cross-agglutination of the *Brucella* and *Bacterium tularense* should be borne in mind. In an investigation of 70 cases of tularemia, the writer<sup>36</sup> has found 6 instances in which such cross-agglutination occurred. In these cases, the relatively higher titer with the *tularense* antigen and the typical clinical history of tularemia left no doubt as to the proper interpretation of the serological findings. Francis and Evans have suggested that all serums from suspected cases of tularemia or undulant fever should be tested for both antiabortus and antitularense agglutinins, unless the clinical history points definitely to a recognized source of infection for

undulant fever or tularemia. If it should develop that the *abortus* and *tularensis* titers are the same, or nearly so, agglutinin absorption tests will distinguish between them

We have observed no cross-agglutination with any organism other than *Bacterium tularensis*. Nicolle found no cross-agglutination in patients suffering from a variety of non-*Brucella* diseases, principally typhoid fever, malaria and incipient tuberculosis. Occasionally, non-specific agglutination occurs in low titer in uninactivated serums, the pseudoagglutinins will disappear when the serum is inactivated (56° C for 30 minutes). In over one-half of our cases, a complete Widal agglutination test has been carried out. The Widal reaction was positive in low titer in only 2 cases—in individuals who had previously been inoculated with the triple typhoid vaccine. In view of the clinical similarity between typhoid fever and undulant fever in occasional cases, it is desirable to make it a routine practice to test for anti-*abortus* agglutinins in all negative Widal tests. This practice was instituted in our laboratory two and one-half years ago, with the result that 12 cases of undulant fever have been discovered in this manner.

In routinely testing serums for the presence of both anti-*abortus* and anti-*melitensis* agglutinins, we have encountered no essential difference in the agglutinin titers. It is, therefore, quite unnecessary to employ the two antigens routinely.

Besides the agglutination test, there are 3 other procedures which may be employed as a means of confirming a

clinical diagnosis of undulant fever, namely, (1) the isolation of the organism from the blood, urine or feces, (2) animal inoculations, and (3) the intradermal test.

### *Cultural Studies*

Fifteen to twenty cc of blood should be collected for culture at the peak of one of the pyrexial waves, and placed directly in flasks containing 30 cc of infusion broth, varying the amount of inoculum in each flask from 1 to 3 cc. Subcultures should be made from the fourth to the twentieth day on beef liver infusion agar or glucose agar, incubated in a partial anaerobic chamber containing about 10 per cent carbon dioxid. Small "dew-drop" colonies usually appear on the agar slants in two to four days. After 2 or 3 transfers the organism usually grows well aerobically. Certain strains of the organism, particularly the porcine type, will grow well in the absence of carbon dioxid tension. The likelihood of recovery of the organism from blood cultures is not as great as in some other bacteremias. In one of our cases, the organism was finally recovered from the blood after 6 negative results. In hospitalized patients, it is possible to do daily blood cultures; in such cases, the likelihood of isolation of the *Brucella* is much greater than in patients cared for at home, where complete laboratory studies are rarely carried out. It is significant that we succeeded in recovering the organism from seven of ten patients admitted to the hospital. Urinary specimens for culture should be collected through a sterile catheter. The technique for the recovery of the

organisms from feces has been fully described by Amoss.<sup>81</sup>

The danger of laboratory infection is very great. Five workers in the Hygienic Laboratory of the United States Public Health Service have acquired the infection during the course of their investigations of undulant fever. Huddleson has reported 2 cases of laboratory infection occurring in his co-workers

### *Animal Inoculation*

Guinea pigs may be inoculated intraperitoneally with the patient's blood or saline suspensions of macerated tissues. Specimens of heart's blood of the guinea pig may be withdrawn at intervals in order to test for anti-*abortus* agglutinins. Six to eight weeks should elapse before autopsy. Loss of weight, the presence of enlarged joints, enlarged testes and seminal vesicles, whitish foci of necrosis in the enlarged liver, spleen and lymphonodes should be noted. Cultures should be made from the lungs, liver, spleen, kidneys, testicles and lymphnodes.

### *Skin Test*

Because of the fact that there are occasional cases of undulant fever in which repeated agglutination tests are negative, there appears to be need for a more delicate test to supplement the agglutination test. Several recent reports indicate that the intradermal test holds considerable promise as a diagnostic aid in those cases in which blood cultures and agglutination tests are negative. Burnet<sup>40</sup> regards the test as more reliable than the agglutination method. Mitra<sup>41</sup>, Bua<sup>42</sup> and Trenti<sup>43</sup> have found that the intradermal injection

of saline suspensions of killed *abortus* organisms gives specific cutaneous reactions. King<sup>6</sup> has experienced encouraging results in the application of the intradermal reaction to guinea pigs and monkeys previously infected with *Brucella abortus*. Fleischner, Meyer and Shaw<sup>44</sup> regard the test for cutaneous hypersensitivity in guinea pigs as highly specific; identical skin reactions were obtained when the disease was produced by either the *abortus* or *melitensis* varieties. Giordano<sup>45</sup> has carried out a controlled study of the value of the test in 25 proved cases of undulant fever, with uniformly successful results. In 28 of the Dayton patients, whose serums agglutinated *Brucella abortus* in titers ranging from 1:40 to 1:2560, strongly positive skin tests were obtained in every instance. Thirty-six patients suffering from a variety of other diseases gave entirely negative results. We have injected intradermally 0.1 cc. of a saline suspension of heat-killed *abortus* organisms, adjusted to the standard used in the preparation of the *abortus* vaccine (2 billion per cc.). In earlier studies we used larger doses of a stronger suspension, adjusted to the silica turbidity standard, but we encountered several severe general and local reactions. A positive test is characterized by the gradual development of an indurated red area at the point of inoculation, within 12 to 36 hours after injection. In some cases, a mild transient ascending lymphangitis develops. In the center of the indurated area a pin-head to match-head size, soft, yellowish granuloma developed in about one-

third of the patients. Smears and cultures from this softened area have revealed no organisms and only an occasional pus cell. The indurated area usually persists for weeks or months. A mild elevation of temperature and a slight accentuation of the symptoms usually follows the injection. In all but 4 cases, the agglutinin titer was found to be increased after the intradermal test. In 7 of our cases we have found strongly positive specific skin reactions in patients in whom a clinical diagnosis of undulant fever had been made, but whose blood serum showed no antiabortus agglutinins on repeated examination. Specific vaccine therapy produced as effective a response in these cases as it did in the patients from whom the organism was recovered and whose serum showed antiabortus agglutinins in high titer. Similar results were obtained in 4 patients with agglutinin titers of 1:40. In the present state of our knowledge, it would be unwise to utilize the skin test as the only diagnostic method. It should be regarded only as an adjunct to bacteriological and serological studies.

#### Treatment

The most important consideration in the control of undulant fever is prophylaxis. Veterinarians have long been aware of the widespread distribution of *Brucella* infections among cattle and other domestic animals. They have become more acutely conscious of its economic importance since the etiologic relationship of contagious abortion in animals and undulant fever in man has been established. Since the disease is so widespread among cattle, it will require many years of diligent

effort to control the infection at its source. It is now generally recognized that contagious abortion is of more frequent occurrence and a source of greater economic loss than bovine tuberculosis. Ward Giltner,<sup>46</sup> Dean of the Division of Veterinary Medicine, Michigan State College, recently stated: "It cannot be said that bovine infectious abortion is under control or that it is being subjected to intelligent and effective attempts at control except in a few isolated herds." While veterinarians and public health workers are striving to check the spread of the infection among animals, there seems to be but one logical method for preventing the transmission of milk-borne infection to human beings, and that is by pasteurization. To quote Dr. John R. Mohler, Chief, Bureau of Animal Industry, United States Department of Agriculture: "Infectious abortion is so widespread and the milk of so many animals is infected that the main dependence for protection against whatever danger there may be from *Bact. abortus* in milk must be placed in pasteurization which if properly done will make the milk safe until the dairymen can eradicate the disease from their herds." Our present knowledge of the widespread distribution of undulant fever adds another convincing argument to the many valid reasons which have developed in the past for the universal pasteurization of milk and other dairy products. Zwick and Wedeman<sup>47</sup> found that *Brucella abortus* was killed in 10 to 15 minutes at 60° C, and in 5 to 10 minutes at 65° C. Park<sup>48</sup> mixed several strains of *Brucella abortus* isolated from cattle and swine with cultures of *Brucella*

*cella melitensis*, and made a milk suspension containing 5,00 million bacteria per cubic centimeter; these organisms were killed when exposed to 140° F. for ten minutes, to 142° for seven minutes and 145° F. for five minutes. Boak and Carpenter<sup>49</sup> found that while 8 strains of *Brucella abortus* of porcine, human and bovine origin, grown in milk, varied in their thermal death point, an exposure of 15 minutes at 140° F. destroyed the human and bovine cultures, the porcine strain, while somewhat more resistant, was destroyed in 20 minutes at 140° F., 15 minutes at 142° F. and 10 minutes at 145° F. It is apparent, therefore, that complete pasteurization (143-145° F. for 3 minutes) will destroy the *Brucella*. The need for strict supervision of the pasteurization process is apparent.

The treatment of the disease in human beings has been essentially directed towards alleviation of the prominent symptoms. Chemotherapeutic measures and specific vaccines and antisera have been employed in a minority of cases.

Mercurochrome and acriflavine have been used intravenously in a small number of cases. Most of the reports are too meager to warrant conclusions. In about one-half of the cases in which mercurochrome has been employed, the results were regarded as favorable; in the remaining cases it was regarded as of doubtful benefit or useless. Ross and Martin<sup>50</sup> found that mercurochrome had no direct effect *in vitro* upon *Brucella melitensis* and *Brucella abortus* in concentrations which it is possible for these organisms to achieve in the blood stream. The

employment of acriflavine has not produced uniform results. In a disease characterized by spontaneous remissions, the therapeutic value of any agent is open to question. Mercurochrome was used in 6 of our cases and acriflavine was tried in 5 cases, without any appreciable effect on the course of the disease. Neoarsphenamin was ineffective in 2 cases.

Many observers [Bassett-Smith,<sup>51</sup> Auricchio,<sup>52</sup> Angle,<sup>53</sup> Helwig,<sup>54</sup> Cumston,<sup>55</sup> De Finis,<sup>56</sup> Giuffre,<sup>57</sup> Khaled<sup>58</sup> and Prausnitz<sup>59</sup>] have reported favorable therapeutic results with specific vaccine therapy. Nicolle and Conseil<sup>60</sup> have found that subcutaneous injections of vaccine will protect human beings against subsequent injection of living organisms. Burnet immunized two monkeys with *Brucella abortus*, one with a living culture, the other with a killed culture; subsequent inoculation with living cultures of *Brucella melitensis* produced no effect.

In 46 of our cases, we have utilized a vaccine made from heat-killed *Brucella abortus*, standardized to 2 billion per cc., with such apparently favorable results that we are now employing it as a routine treatment. The vaccine is given by deep subcutaneous injection. The usual dosage has been one-fourth cc. for 3 injections, followed by one-half cc. for 3 injections, followed by 1 cc. doses—all at 3 day intervals. The first one or two injections have been followed by a mild or moderately severe general reaction in two-thirds of our cases, following which the reactions have diminished in intensity after each succeeding vaccination. In several instances the site of injection remained indurated for

many days, no necrosis or abscesses developed

Following the first two or three injections, the fever usually approached the normal level and the symptoms abated. As a general rule, those patients who experienced the most marked general reaction had a most rapid favorable response to the vaccine.

In order to determine whether or not the results obtained were entirely due to a foreign protein, typhoid vaccine was used in 8 cases and sterile milk was used in 4 instances. In these cases, there was a much more marked elevation of temperature following the injections, but the subsequent course of the disease was not appreciably altered.

Further investigations of the efficacy of the *abortus* vaccine are in progress. It is hoped that other workers will give the *abortus* vaccine a thorough clinical trial and report their observations. Due caution must be exercised in the evaluation of any therapeutic measure in a disease characterized by natural remissions.

### Summary and Conclusions

1. Undulant fever is a common and widespread disease of man. The writer reports herewith the clinicopathologic findings in 90 cases of undulant fever, encountered in and about Dayton, Ohio, during the past 18 months. Approximately 2000 cases of undulant fever have been recorded by state health departments during the past 2 years.

2. The etiologic unity of contagious abortion in cattle and other domestic animals and undulant fever in man has been conclusively demonstrated.

The manifestations of *Brucella* infection (*Brucellosis*) in animals and man show a distinct parallelism.

3. No cases of direct porcine or caprine origin were encountered in the series of cases which forms the subject of this report. Both the porcine and bovine strains of *Brucella abortus* are capable of producing the disease in human beings. No definite dividing line distinguishes the degree of pathogenicity of any of the *Brucella*. Available evidence indicates that the great majority of the cases of undulant fever in this country have been the result of the ingestion of raw milk or unpasteurized dairy products containing some variety of the genus *Brucella*. The skin is probably an occasional portal of entry in those whose occupation (veterinarians, farmers, meat handlers) brings them in direct contact with infected animal tissues.

4. Contagious abortion of cattle is widely prevalent in all parts of this country. The disease exists among non-pregnant cattle and bulls, some pregnant cows with the infection do not abort. Calves appear to possess a relative immunity. *Brucella abortus* has been recovered from the milk of cows whose serum showed no anti-*abortus* agglutinins.

5. In man, undulant fever is frequently confused with typhoid fever, malaria, influenza and tuberculosis, less often it is confused with acute rheumatic fever or subacute bacterial endocarditis. Contrary to the general belief that an original clinical diagnosis of undulant fever is made with great difficulty, several Dayton physicians made an initial clinical diagnosis of this disease in nearly one-half

of our cases. An analysis of the manifestations of the disease in man, based upon a clinical survey of our patients, reveals a more or less characteristic clinical picture.

6. The distribution of the disease among male and females was about equal in our series of cases. Children appear to possess a relative immunity to the disease. Only 15 percent of our patients were engaged in occupations which would bring them in direct or indirect contact with cattle or hogs; all were raw milk consumers.

7. Even though the name "undulant fever" implies recurring febrile remissions and relapses, these were observed in only 11 of our cases. One-fourth of our patients experienced a short, mild illness; such cases are easily confused with influenza.

8. No evidence of man-to-man infection was observed.

9. Joint symptoms were an important feature of the disease in one-third of our cases. The frequent occurrence of abdominal pain has led to mistaken diagnoses of appendicitis or cholecystitis.

10. *Brucella abortus* apparently exhibits the same predilection for the genital tract of human beings as it does in susceptible animals. There is considerable evidence that the disease may produce human abortion. The organism is capable of producing seminal

vesiculitis, prostatitis, epididymitis and orchitis in man.

11. Leucopenia with lymphocytosis is a characteristic blood finding.

12. The average duration of illness in our series was approximately four months. Fatal termination is rare, having occurred in but one of our cases.

13. Many human beings appear to possess an immunity to the disease. The degree of virulence of the *Brucella* varies widely.

14. Four methods are available for the confirmation of a clinical diagnosis of undulant fever: 1. agglutination test, 2. blood and urine cultures, 3. animal inoculation, 4. skin test. The simplest method is the agglutination reaction. The rapid agglutination method, using Antigen-Huddleson, is a reliable procedure. No arbitrary serum agglutinin titer can be regarded as diagnostic of the disease. In about five per cent of human beings with undulant fever, no antiabortus serum agglutinins are present. Blood cultures should be obtained whenever possible.

15. The skin test gives promise of being a reliable adjunct to the agglutination test.

16. The abortus vaccine appears to possess considerable therapeutic value.

17. Complete, carefully supervised, pasteurization of milk and dairy products is the logical means of eliminating milk-borne infection.

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# Psittacosis

## A Clinical and Pathological Report of Three Cases\*†

By W W. G MACLACHLAN, M.D., *Pittsburgh*, H. H. PERMAR, M D ,  
*Pittsburgh* and C A ROGERS, M D., *Freeport*

THE opportunity to make some clinical and pathological observations on psittacosis was afforded when a small group of three cases in one family was recognized by one of us in his practice (C.R.). One patient, a woman of 53 years, died and an autopsy was performed. The other two cases, a girl of 22 and a child of 9 both recovered. The fatal case presented the appearance of pneumonia but the recovered cases were typhoidal in character, the older girl being very ill for 28 days while the child showed a very mild infection of about two weeks' duration

A parrot had been given to the patient who died, as a Christmas gift, on December 23, 1929. It was sick when bought, both the buyer and seller being aware of this fact. It had a bronchial infection and a diarrhea. The parrot died on December 30, 1929. Three members of the family did not become ill, although one of them, a young man of 25, had more to do with the parrot than anyone else

in the household, as he fed it, cleaned the cage and finally buried it

### *Clinical History of the Three Cases*

1. Female, age 53, became ill January 2, 1930 with a chill, intense headache, vomiting and a feeling of great tiredness. She had been perfectly well the day before. Headache, vomiting and weakness continued, and about the sixth day of the disease, delirium developed. A harsh, dry unproductive cough appeared on the fifth day and was present to the end, increasing in intensity. There was no expectoration. There was no pain in the chest at any time. From the onset the temperature was high, 104-105, the pulse rate relatively slow, 90-100, until the eighth day of the disease when it became rapid, 120-140, and remained so until death. The respirations were 24 until the sixth day and then gradually increased up to 50 in the latter days of the illness, but even to the end there was no cyanosis and no marked abdominal distention. On the eighth day she developed incontinence of bladder and bowels. The physical signs in the lung were practically negative for the first five days, except for a very few

\*Read before the Association of American Physicians, Atlantic City, May 1930.

†From the Department of Medicine, University of Pittsburgh and Pathological Laboratory of Mercy Hospital, Pittsburgh.

râles at the right base, but after this signs of consolidation developed and were heard over all the lobes on the right side and at the base of the left lower lobe. Many râles developed on the ninth and tenth day. The spleen was never palpable. The white blood count was 6,200. A pleural rub was never found. The patient died on January 12, 1930 on the tenth day of the disease.

2 Female, age 22, complained of severe headache and tiredness with nausea and vomiting. Illness began January 4, 1930. At onset the temperature was 104.2, pulse 90, respirations 26. Vomiting persisted throughout her twenty-eight days of illness. The temperature and pulse rate for four weeks, except the last two days, was about the same as at the onset. The fever fell to normal almost as quickly as in a crisis. There was no palpable spleen, no rash, and no pain in the chest suggesting pleurisy. A harsh, for the most part dry, hacking cough developed about the fifth day and persisted to the end. No cyanosis was present. Some white, slightly purulent sputum was occasionally noticed. On the eighth day there was a suggestion of consolidation at the apex of the right lower lobe, (voice sounds increased over the small area and a very few râles). At no other time were the signs more evident, although a few scattered râles could be heard after coughing over both lower lobes of the lung during the second and third week. Patient was delirious for almost the last two weeks of her illness and had incontinence of bladder and bowels during this period. There was no diarrhea. The blood

counts during the illness were as follows

Jan 12, 1930 Hemoglobin 86 per cent, red blood cells 4,300,000, white blood cells 5,400, polymorphonuclears 69 per cent, large lymphocytes 7 per cent and small lymphocytes 25 per cent

Jan 18, 1930 Hemoglobin 89 per cent, red blood cells 4,360,000, white blood cells 5,600, polymorphonuclears 81 per cent, large lymphocytes 10 per cent and small lymphocytes 15 per cent

Jan 29, 1930 Hemoglobin 65 per cent, red blood cells 3,840,000, white blood cells 5,600, polymorphonuclears 78 per cent, large lymphocytes 7 per cent and small lymphocytes 15 per cent

A trace of albumin was present in the urine. Blood cultures on three occasions were negative. The blood serum on the twenty-second and on the twenty-eighth day of the disease showed a negative agglutination test with the B typhosus, B paratyphosus and B aertrycke. On the twenty-second day a B. acidilactici was isolated from a specimen of sputum and this organism was agglutinated on two occasions by the patient's serum in 1-160 dilution. Dr. George Lacy who kindly did this part of the work for us regarded this observation as a non-specific one and of no significance. The patient was febrile for twenty-eight days but made a quick and uneventful convalescence.

3 Female, age 9, was taken ill on January 12, 1930 with headache and tiredness. She was sick for about two weeks, but was very mild, all compared with the previous case. Temperature for a few days was between 103-104 but gradually fell to normal level in the course of 2 weeks. Pulse and respirations were 90 and 26 respectively.

within normal limits. She had very little if any cough, nor any abnormal physical signs in the lungs. There was no diarrhea nor any vomiting. The symptoms of headache and tiredness lasted a little over a week. The spleen was much enlarged and was palpable for three weeks after the onset of her illness. This was the one outstanding physical sign. The blood counts were as follows.

Jan 16, 1930 Hemoglobin 75 per cent, red blood cells 3,640,000, white blood cells 4,600, polymorphonuclears 62 per cent, large lymphocytes 7 per cent, and small lymphocytes 31 per cent

Jan 29, 1930. Hemoglobin 70 per cent, red blood cells 4,160,000, white blood cells 9,400, polymorphonuclears 41 per cent, large lymphocytes 7 per cent, small lymphocytes 49 per cent, eosinophiles 2 per cent and basophiles 1 per cent

The urine was normal. A blood culture was negative. Blood serum agglutination was negative for *B. typhosus*, *B. paratyphosus* and *B. aertrycke*. Her blood serum also agglutinated the *B. acidilactici* which was isolated from the sputum of Case 2 in 1-160 dilution, but this was not regarded by Dr. Lacy as a significant finding. She made a good recovery.

#### AUTOPSY OF CASE 1.

The body was embalmed. It was that of a large, well developed and well nourished woman. There was nothing noteworthy in the general appearance. The right pleural sac showed many dense fibrous adhesions which were broken down with some difficulty. There was no fibrin on the surface of the lung and no fluid in the pleural cavity. The left side of the thorax was quite clear. The pericardial sac was small and free from fluid. The peritoneal cavity showed no fluid, but a very fatty mesentery, containing small mesenteric lymph nodes. The spleen could not be seen.

The edge of the liver was apparent just below the costal margin. No edema of extremities was present.

*Right Lung:* The whole of the lung had a dark red color and the greater part of the lower lobe, the anterior portion of the middle lobe along the superior border, and the upper part of the upper lobe were firm and definitely consolidated. Air-containing lung substance was present between these solid portions. On section, the cut surface was a deep red color, except in the upper lobe where a more grayish appearance was noted. The lung was not a wet lung in the embalmed state. The air-containing substance lying between the consolidated patches was dark in color, due to congestion and anthracosis. The lining of the bronchi was not remarkable. The P. B. lymph nodes were negative.

*Left Lung:* The base of the left lower lobe was firm and on section showed a dull red consolidated area. The rest of the lung was air-containing, and of a dark slate color, due to anthracosis. The consolidation in the left lung occupied only about one-fourth of the lower lobe. The P. B. lymph and bronchi were normal in the gross. The lung was dry.

*Hearts:* The heart was small and its chambers were contracted. The valves appeared quite normal, as did also the heart muscle.

*Aorta:* The aorta showed some intimal thickening about the intercostals, but was very clear otherwise, save that there was a little fatty intimal change.

*Stomach and Intestines:* The stomach and intestines were quite normal. There was a pale lining to the whole of the small bowel, and no evidence of hyperplasia of the Peyer's patches or solitary follicles was seen. The mesenteric lymph nodes were not enlarged.

*Liver:* The organ was of normal size and appearance. On section, the cut surface was a little pale, but the substance appeared to be normal. There was no change noted in the gall bladder wall, although the organ contained one smooth, pale cholesterol stone.

*Spleen:* The spleen was quite double the normal size. It was of a deep purple red color and the cut surface was smooth and

dull red with very indistinct Malpighian bodies showing against the red pulp. The tissue of the spleen was firm, undoubtedly due to the embalming.

**Kidneys** The kidneys were somewhat contracted, showing a roughened, irregular, granular cortex with geographical scarrings when the capsule was stripped. The peripelvic tissue was fatty and slightly increased in amount. On section, the cortex was narrowed. Pelvis of kidney was normal.

**Pelvic Organs** There were some pelvic adhesions, but the uterus and adnexa appeared to be normal.

### ANATOMICAL DIAGNOSIS PSITTACOSIS

BRONCHO-PNEUMONIA, (Bilateral)  
OLD PLEURAL ADHESIONS,  
RIGHT

ACUTE TOXIC SPLENITIS WITH  
ENLARGEMENT

SUPERFICIAL FATTY STREAK-  
INGS OF AORTIC INTIMA

CHOLELITHIASIS

CHRONIC NEPHRITIS (A S)

PELVIC ADHESIONS, SLIGHT

### MICROSCOPICAL

**Lungs** Sections of the lungs showed an acute inflammatory reaction in various stages of development. The earliest stage was an inflammation of the bronchioles, with an exudate of polymorphonuclear leucocytes and endothelial cells (phagocytic mononuclear leucocytes), mingled with granular precipitate. The epithelial linings of the bronchioles remained intact. The vessels of the bronchiolar walls and of the adjoining alveoli were engorged. The lymphatics showed some dilatation, but contained only granular precipitate with no cellular exudate.

Large areas of the lung were in a state of partial collapse. Here also the bronchioles were filled with acute cellular exudate. The deflated alveoli had unusually thick walls, due partly to engorgement of their capillaries, and partly to a remarkable prominence of the respiratory epithelium. This reaction was the most striking single finding in the lung. The epithelial cells were much enlarged and protruded into the

air spaces. Mitotic figures were commonly found in them. The alveolar exudate consisted chiefly of large mononuclear cells, (endothelial leucocytes), many of which were phagocytic for carbon or cell debris. Occasionally an irregular, slightly flattened large epithelial cell was found in the free exudate. These were not phagocytic, instead, they showed evidences of disintegration. The epithelial cells were identified by their location on the alveolar wall, the greater size of the cell, the larger and more vesicular nucleus and larger nucleolus, as well as the absence of phagocytosis. The use of a Romanowsky stain, (McNeal), on the tissues showed a light blue cytoplasm in the epithelial cells, and a denser pink cytoplasm in the phagocytic mononuclear cells of the exudate. A few polymorphonuclear leucocytes and moderate numbers of red blood cells were mingled with the exudate. Various quantities of granular precipitate were found. There was no evidence of interstitial inflammation, though the lymphatics were dilated by edematous fluid. The pleura showed no reaction where it overlay the lung in this state.

The most acute inflammation was characterized by the elements described, with the addition of various amounts of fine, thready fibrin, moderate numbers of polymorphonuclear leucocytes and a considerable amount of granular precipitate. The enlargement of the alveolar epithelium, with mitosis in many of the epithelial cells, was just as evident here as it was in the partly collapsed areas. Here again, interstitial inflammation was lacking, save for widening of the lymphatics by edematous fluid. However, in one section a small vessel showed recent thrombosis and a few polymorphonuclear leucocytes in its wall. The bronchioles showed acute exudate. The pleura was not involved though the interstitial inflammatory reaction was present immediately under the pleura.

**Heart** The sections of the heart showed no evidence of inflammation and were free from thrombosis. The endocardium was normal. The myocardium showed some degenerative changes. The pericardium was normal.

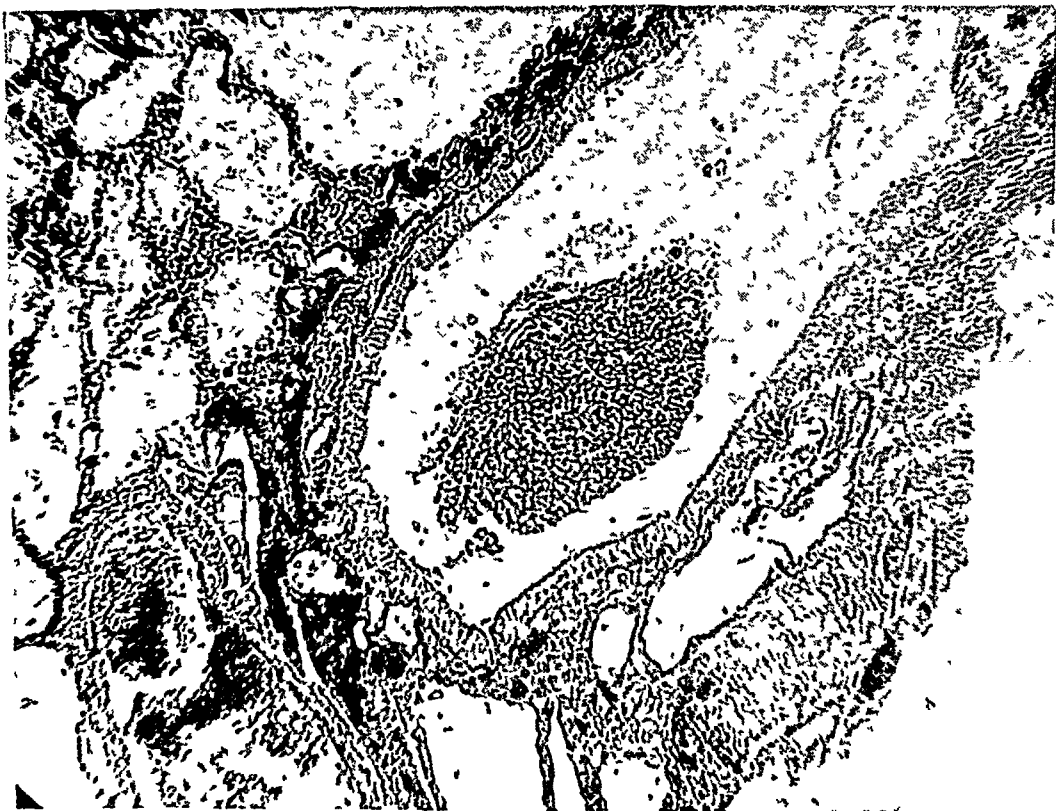


FIG 1 Bronchiole shows a plug of exudate, and surrounding alveoli are clear. Some engorgement of vessels and dilation of lymphatics. Low power.

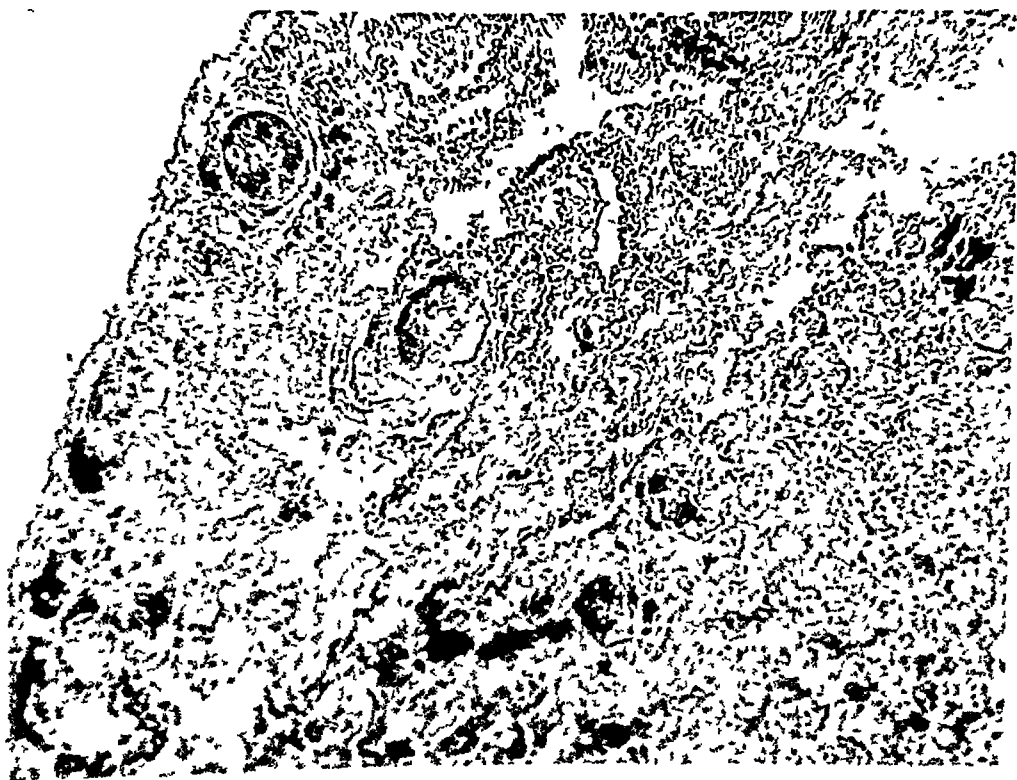


FIG 2 Lung shows collapse with congestion of vessels, thickening of alveolar walls and pleura not involved. Low power.

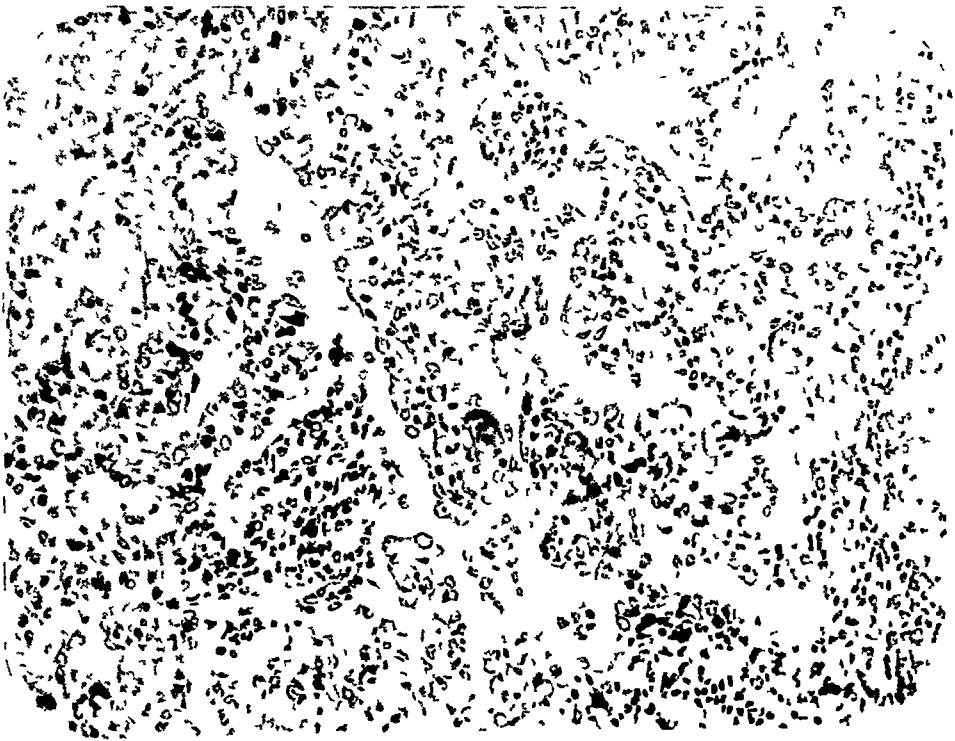


FIG. 3 Higher magnification of the collapse of lung shows widening of alveolar walls with congestion of capillaries, prominent alveolar epithelium and mononuclear exudate in alveoli



FIG. 4 Lung shows a more acute exudate with prominent granular precipitate in addition to mononuclear phagocyte cells.



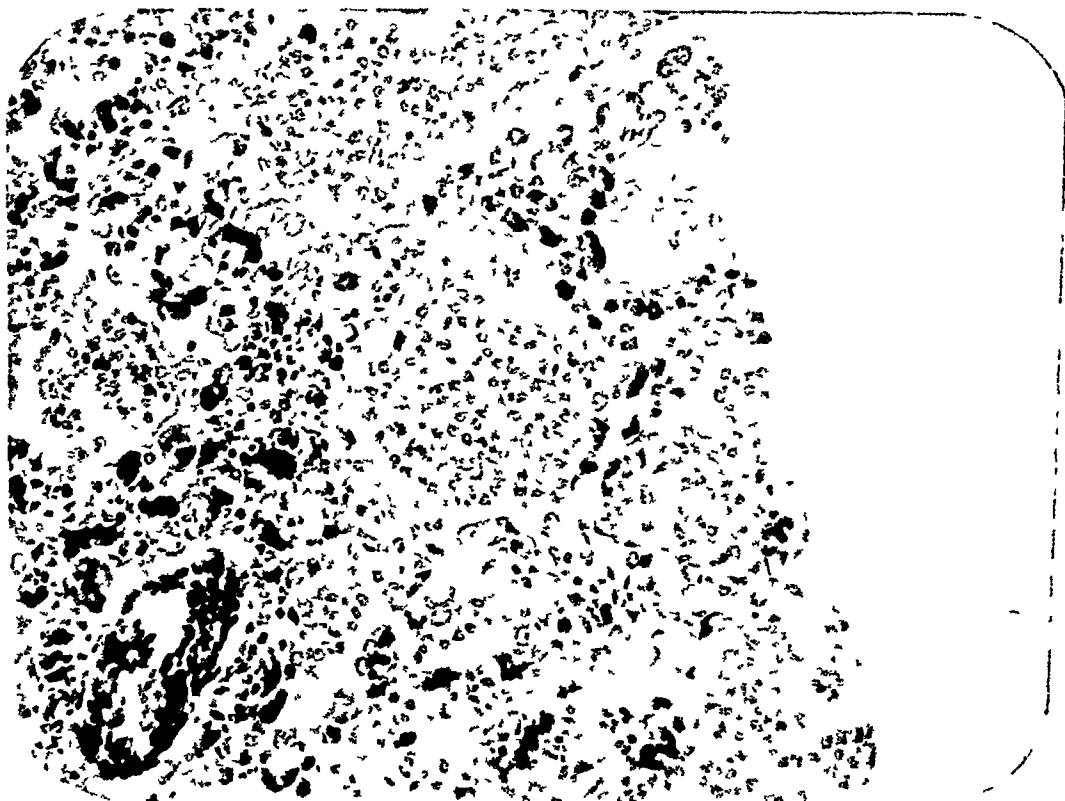
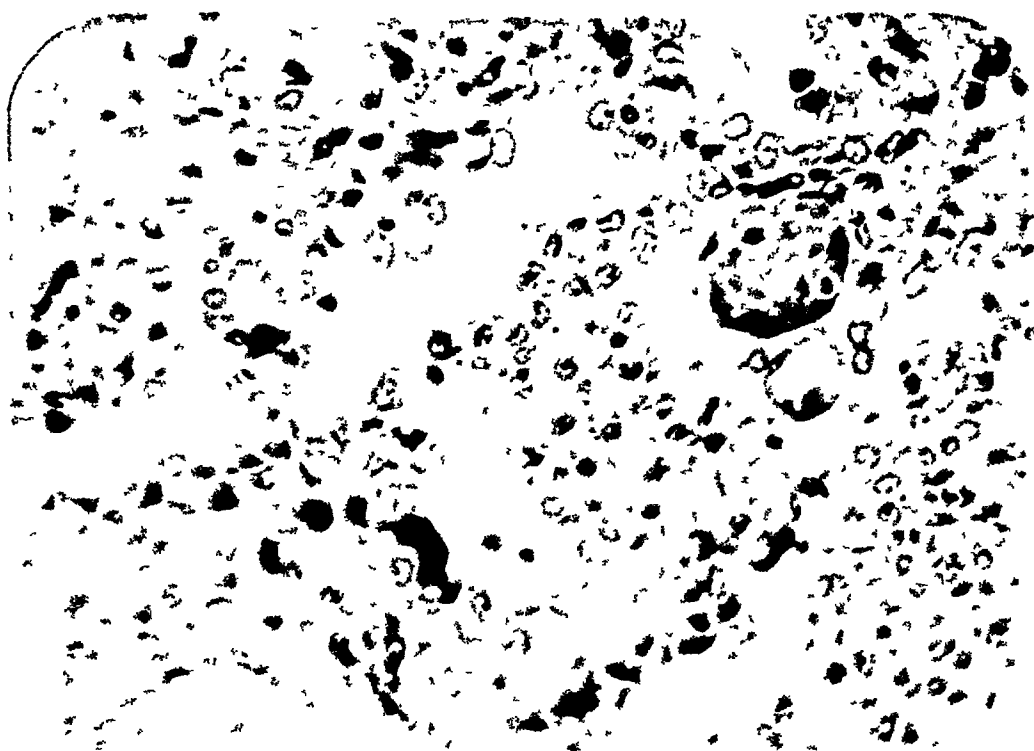


FIG 5 Lung shows moderate collapse with thickened alveolar walls, capillary congestion and mononuclear exudate. No interstitial inflammation is present. Low power.



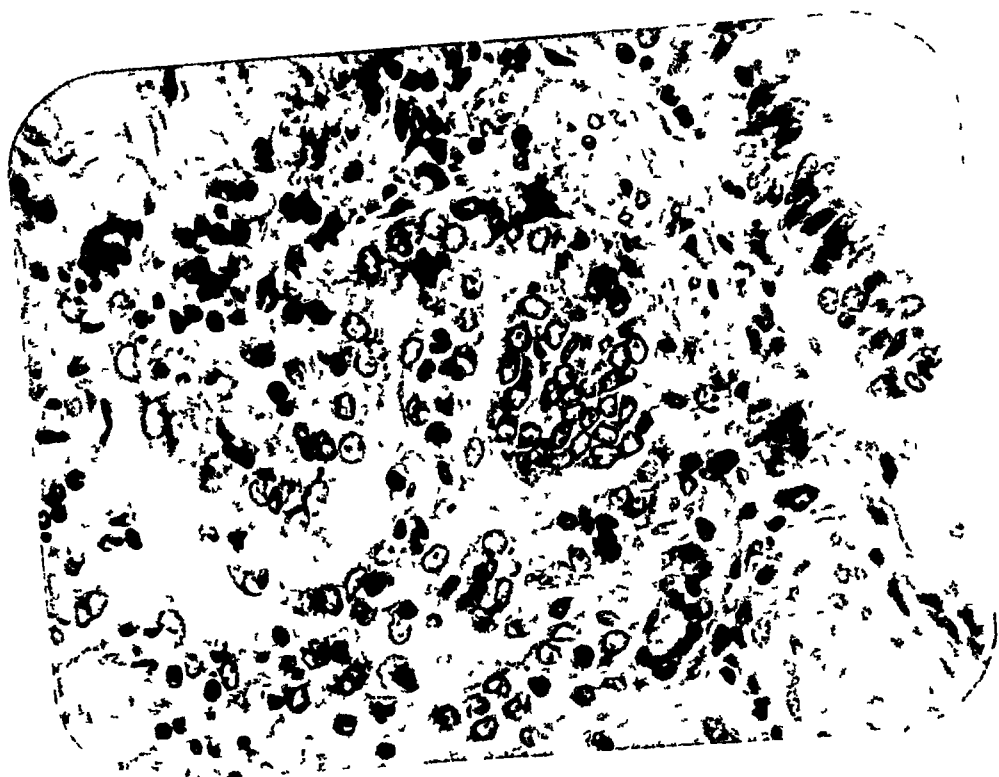


FIG 7

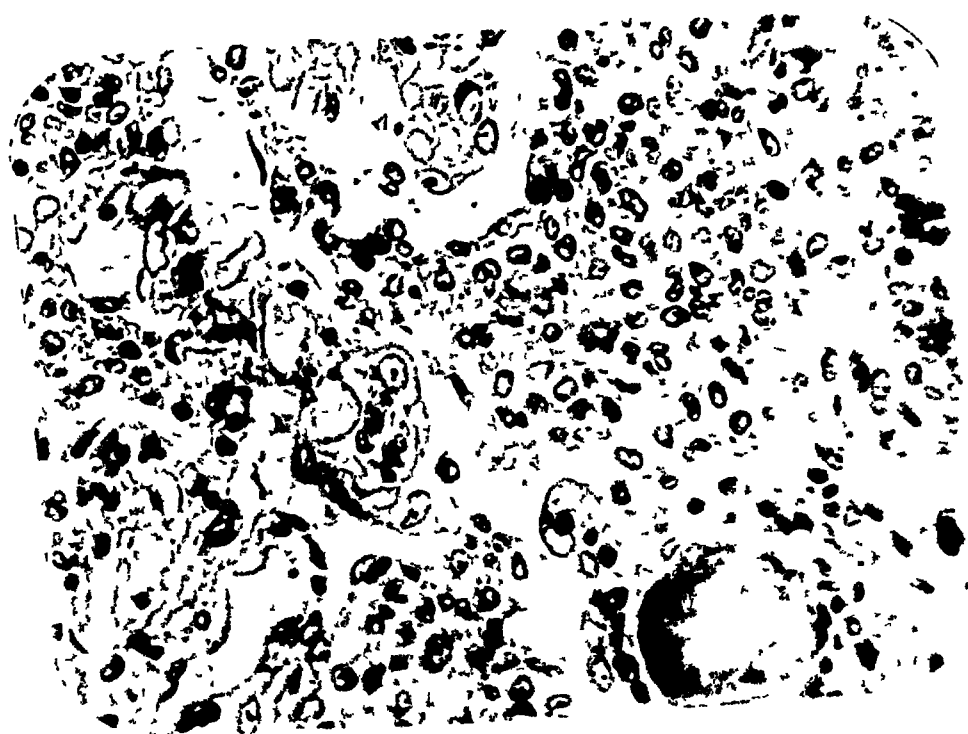


FIG 8

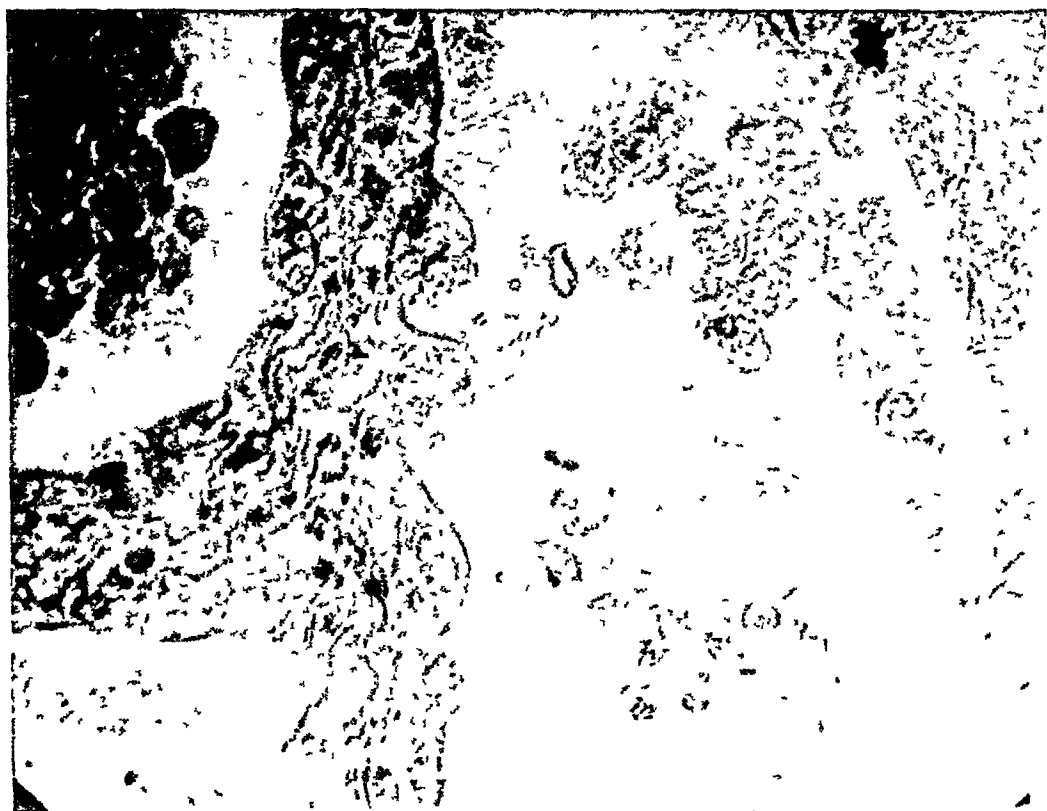
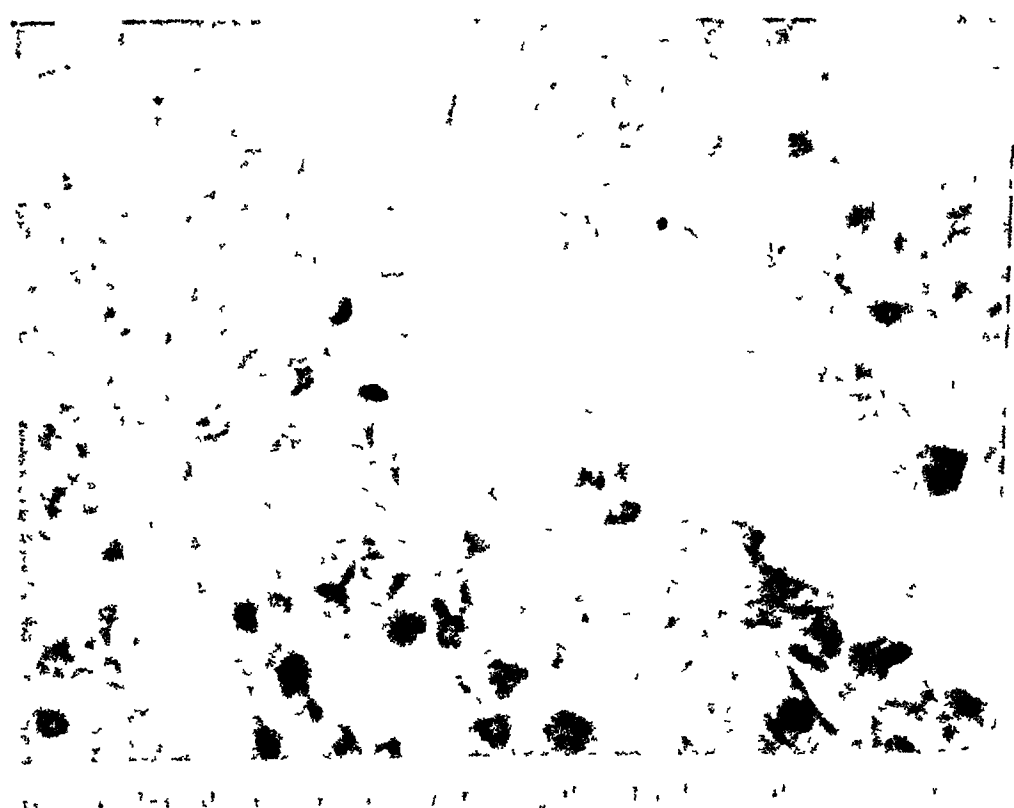


FIG 9 High power of lung shows the very prominent epithelial lining cells of alveoli



degeneration The von Kupffer cells were slightly more prominent than usual

*Spleen* The outstanding finding in the spleen was extreme engorgement of the sinuses of the pulp There was no evident increase in free mononuclear cells in the spleen The endothelial cells lining the sinuses were prominent

*Kidney* The sections of the kidney, like those of the heart and liver, showed well marked toxic degenerative changes In the cells of the convoluted tubules of the cortex were found cloudy swelling, with pyknosis and karyorrhexis in the nuclei

In résumé, the pulmonary inflammation may be termed a mononuclear broncho-pneumonia, and the outstanding peculiarity of the reaction is the unusual hypertrophy and hyperplasia of the respiratory epithelium throughout the involved lung The bronchioles show acute inflammatory exudate Partial collapse of the lung tissue is evident, while interstitial inflammation and extension to the pleura are lacking The changes in other organs are essentially those associated with an acute infection and its accompanying toxæmia

The first reference to the disease parrot fever, (Morange in the Paris epidemic of 1894 gave the name Psittacosis from the Greek word *ψιττακος*, a parrot), dates from 1879 when Ritter, in Switzerland, described a group of 7 cases Three of this number died and autopsies were done by Eberth The clinical description of the cases that Ritter reported is quite similar to what was later noted by others and also to the reports of the present epidemic He believed that the human was infected by some unknown germ which was transmitted by the parrot or other tropical birds He noted the pneumonic and typhoidal-

like clinical courses of the disease and he emphasized the fact that the pneumonia clinically was not the usual type of pneumonic infection The pathology of the lung is not reported in great detail by Eberth but he does refer to one finding in the microscopic study, namely, the presence of many desquamated lining alveolar cells in the exudate of the pneumonia At that time, however, it is likely true that all mononuclear cells in lung exudate were considered as being of epithelial origin from the lining cells of the alveoli, but one can say that the original paper of Ritter gave a very accurate clinical picture of the disease and also mentioned, although briefly, what we regard as one of the important microscopic features of the lung lesion In 1892 to 1896, many cases of the disease were reported in Paris and a number of papers written on this subject According to Desjardin-Beaumetz, who at first considered that the disease was la grippe, upwards of 70 cases with a little over 30 per cent mortality were recorded The epidemic followed the importation of South American parrots Nocard, in 1893, described a gram negative bacillus which he called the B psittacosis It was isolated from the marrow of the bones of wings which had been saved from birds having died of the disease during the previous year During the same epidemic Morange, Gaston and Netter found pneumococci and Friedlander's bacillus in the lungs of human cases dying with psittacosis In 1896, Gilbert and Fourmer confirmed Nocard's work, finding the B psittacosis in the parrot and also in the heart's blood of a patient

dying from psittacosis. They believed the bacillus psittacosis of Nocard was of the paracolon or paratyphoid family. The most detailed early pathological report is by Melenchini who studied a group of cases in 1895 in Florence, following an importation of South American parrots from Genoa with subsequent development of the disease. There is no doubt from his description of the pneumonia, both in the gross and microscopically, that the lesion in the lung was the same as subsequent observers have noted. He refers in detail to the presence of desquamated lining alveolar cells, the small amount of fibrin, the absence of acute pleurisy as a rule and the different picture of this disease from that of ordinary pneumonia. Melenchini frankly doubted the specific nature of Nocard's bacillus. He found pneumococci in the lungs of his cases, but was not certain whether they were the primary infecting agents or merely secondary invaders. He believed that the parrot probably harboured the infecting organism which was transmitted to man, although he put a question mark after psittacosis on the title of his paper. In this country psittacosis was first recognized by Vickers and Richardson in 1901.

Cough was noted and sputum, as a rule, was absent. Weakness, headache, delirium and not much splenic enlargement were noteworthy characteristics. Some cases suggested typhoid. All serological agglutinations were negative. Autopsies showed a pneumonia which Finkler regarded as of streptococcus etiology, as this organism was found in the lungs in the two cases examined. Many mononuclear cells regarded as being of epithelial origin were observed in the alveolar exudate, some polymorphonuclear leucocytes, red blood cells and a little fibrin. The pneumonia was bronchial in type. There was some interstitial inflammation in the lung. These observers did not find the Nocard bacillus and did not believe that it had anything to do with this disease, but, at the same time, they were certain that the etiological agent was a streptococcus transmitted from the parrot. Warthin, in 1917, in a review of psittacosis stated that the etiological factor of the infection was unknown. In 1920, Perry made a bacteriological study of an organism isolated from a sick parrot, (no human case had been infected by this parrot), and found that it was of the salmonella group, of the mutton type of *B. aertrycke*.

land as far back as 1892 but which had never been reported. Thompson in 1929, described four cases, two being fatal. There were no autopsies. In the same year Sailer reported a non-fatal case in this country.

Published studies on the recent epidemic at the time of writing have appeared only in the English and German literature. The present infection appears to have had its origin in the city of Cordoba in the Argentine Republic in July and August 1929. According to Barros, bird dealers congregate there at that time of year to sell parrots which are imported from Brazil and Paraguay. Last year there were many sick birds and subsequently an epidemic broke out amongst the people in Cordoba. The dealers moved to another city, Tucumen, where human cases again developed. Several other towns were similarly infected when the dealers and their parrots appeared. There were probably one hundred cases. The main features of this disease in the Argentine, according to Barros, were as follows: headache, tiredness, rapidly rising fever, vomiting, delirium, intense thirst, relatively slow pulse, no splenic enlargement and variable forms of pneumonia with spasmodic cough but no sputum. In a recent report, (January 1930), Thompson stated that he has records of the existence of 17 more cases, most of whom he has seen. He referred to the sudden onset of the illness, the intense headache, vomiting, diarrhea at times, with marked pulmonary signs later. In some of his cases, on account of the disappearance of breath sounds, fluid was suspected

but could never be demonstrated by needling. Thompson believed, therefore, that there was some obstructive lesion of the bronchi, and referred to the autopsy on one of his cases which confirmed this finding. This observation is interesting in view of the evidence of collapse of lung that we have noted in our sections. The absence of pain in the chest and of sputum are noteworthy. A pleural rub was found only once. Thompson remarked that the presence of the parrot in the history is still essential in the diagnosis. Wilson, who performed the autopsy on Thompson's case, spoke of the exudate as being almost entirely mononuclear. There was no perivascular or peribronchial distribution of inflammatory cells, (no interstitial inflammatory reaction), small bronchi were filled with desquamated epithelium while the larger were clear. Thompson has informed us that the lesion in the lungs, as shown by some of our slides, which Wilson and he have seen, is identical with their own. In one of Thompson's cases in his first report in 1929 a paratyphoid organism was found in a parotid abscess, and in three of his recent cases, from the cages in which the sick parrots had been kept, Lewis has isolated an organism of the salmonella group. Thompson, therefore, believed it inadvisable at present to rule out entirely the possibility of this form of infection. In a discussion of this paper, Hutchinson referred to 22 cases in London in which there were 2 deaths. One case seemed to have been a human contact in that the patients both used the same handkerchief. Horder and Gow have described a

cases. Some of them were not very intimately associated with the parrot and some not at all, but with people who had been in contact with the birds. Areas of necrosis were seen in the lungs of Horder and Gow's cases at autopsy, but the authors refer to nothing particular in the exudate, although they speak of shed alveolar epithelium bordering plugs of coagulate material in some alveoli. Epistaxis and diarrhea were clinical features of their cases. Bedson, Western and Simpson have made bacteriological studies and are the first, as far as we have been able to find, who present evidence to show that psittacosis is a virus disease. They have been unable to isolate any of the salmonella group from cases of this epidemic. In their observation on parrots it is of interest to note that in one parrot a *B. aertrycke* was found but this bird showed lesions in the gross quite different from those having psittacosis, and the organism was isolated with the greatest ease from many sources in the dead animal. The blood from six

ford has reported 5 cases and War-rack one with very definite histories of contact with parrots. Hegler noted cases in Hamburg in July and in November, 1929. In the first group there were 3 cases, 2 being fatal. Clinically, these cases showed delirium, leucocytosis of 11,000-14,000, with broncho-pneumonia. All agglutination tests were negative. At autopsy the exudate in the broncho-pneumonia showed many large desquamated epithelial cells. Some necrotic areas were noted in the lung. The second group were of great interest. A man of 50 died on the 10th day of illness from pneumonia. He had delirium, no cough, no sputum and 4,900 white cells. He had a parrot, but it was not sick. From this patient 5 other cases developed. They were the nurses who attended him in the hospital. All had the same symptoms either of typhoid or pneumonia and 2 of them died, but no autopsies were held. Hegler believed the infection is due to a filterable virus, and that there is evidence of human trans-

cells in alveoli and enlarged spleen. He believed the streptococcus is a secondary infection and that the disease is due to a virus of the filterable type. All agglutination tests were negative.

The only reference at the time of writing to work done in this country is from the Weekly Bulletin of the City of New York Department of Health, in which it is stated that Krumwiede has shown that the infection is caused by a filterable virus.

### *Discussion*

Psittacosis is a rare disease and even during the periods when it becomes epidemic the incidence of infection is not great. It is certainly not a new malady as it was accurately described in 1879 and, as Meyer has suggested, has recurred approximately every decade since that time, although only two fairly wide spread epidemics have been noted, namely, that of 1892-96 in France and Italy, and the present one. With the more or less constant importation of parrots and other tropical birds over periods of years one wonders why it has not been more prevalent, as the disease is so definite that any large number of cases would hardly fail to be recognized. Seemingly the infection is not a constant one in the bird. It is also well to remember that tropical birds other than the parrot may transmit the disease and that the African parrot may also carry the infection as shown by Thompson. Undoubtedly, isolated clinical cases in the past have probably not been recognized, although the microscopic picture of the lesion in the lung is so striking

that one would imagine that it would have been promptly noted by pathologists if it had occurred to any appreciable extent in cases supposedly dying from broncho-pneumonia. The present epidemic has brought out two interesting features with reference to the transmission of the infection. Bedson, Western and Simpson give a very clear description of one human case infected by a healthy parrot, but apparently a carrier of the disease for 14 months. Also human transmission has been spoken of by Hutchison, and Horder and Gow in England and Hegler in Germany. Studies on the epidemiology will probably throw light on this phase of the subject.

The clinical manifestations of the disease from the first description to the present time have shown in all countries a certain general uniformity. There are, of course, variations as one would note in any disease, even as typical an infection as typhoid fever may show the absence of some symptoms or signs. Psittacosis presents three clinical phases which our cases illustrate very well. Firstly, an atypical pneumonia in symptoms and signs, and highly toxic especially for older people, is the most serious form of the infection. Secondly, a very toxic typhoidal state with variable pneumonic features and persisting for three or four weeks, is seen as a rule in younger adults. Thirdly, a very mild infection from a few days to one or two weeks' duration occurs in young adults and children. This type may appear as an influenza or as a paratyphoid or mild typhoidal infection and could easily be overlooked even in epidemic periods. Age seems



to have some bearing on the manifestations and severity of the disease as Horder and Gow have remarked and as our group, infected from a common source, appears to show. In general the more frequent symptoms and signs are as follows. Sudden onset of a high fever with a relatively slow, pulse, intense headache, vomiting and great fatigue. There is a marked tendency to delirium and in the typhoidal types incontinence of bladder and bowels. In the pneumonic forms are found severe cough, very little or no sputum, no pleurisy nor any pleural pain and a delayed appearance of signs of pneumonia. Usually a low or normal white blood count is noted, although some reports indicate a leucocytosis. Agglutination tests and blood cultures are negative. Three of the Berlin cases reported by Meyer showed streptococcus in the blood, but this is the exception. Certainly, from the clinical point of view one does not have a picture distinct enough to establish a diagnosis of psittacosis without a history of the presence of a sick parrot or other tropical bird.

The discussion on the bacteriology had best be left open until more complete reports are available. It would appear as likely that Nocard's bacillus is going to be replaced by a virus infection as the work of Bedson, Western and Simpson in England and Krumwiede in this country have indicated. Further, this view is also held by the German observers, Meyer and Hegler. *Pneumococcus*, *streptococcus*, *B. mucosus capsulatus* and the salmonella groups are probably secondary invaders. The clinical and pathological picture of the disease may be

somewhat influenced by the type of secondary invader.

On account of the fact that psittacosis is a rare infection the opportunity for pathological study of autopsy material has obviously not been great in recent years, although as we have indicated previously in a review of the literature, the lesion in the lung has been described by some early observers in detail in its gross and microscopic picture. It is our belief that the past and present descriptions refer to the same process, although microscopically the interpretation of the mononuclear exudate differs. The older writers believed that these cells were desquamated epithelium from the alveolar linings, our own view, in accord with present opinion, is that they are mononuclear phagocytes, derived from the reticulo-endothelial system. In the gross the pneumonia is as a rule of the bronchial type, persisting in a state of red hepatization even when, from the duration of the disease, a grey hepatization might be expected. Horder and Gow remarked that the lung had the appearance of an infarct, and it is of interest that thrombosed vessels have occasionally been found. The usual absence of fibrinous pleurisy is noteworthy and explains the freedom from pain. A moderate splenic enlargement with intense engorgement, and absence of any hyperplasia of the lymphoid structures of the bowel and mesentery complete the picture. The gross appearance of the tissues at autopsy are, therefore, not as distinctive nor diagnostic as formerly. It is to be kept in mind that the gross findings, both gross and microscopic,

in a case dying on the 10th day, as did our case and one dying in the third or fourth week, might present different pathological features

The inflammatory reaction in the lung may be interpreted as a primary diffuse bronchitis, affecting chiefly the smaller bronchi and bronchioles. The exudate in the air passages causes occlusion of their lumina, after which there is a degree of collapse of the alveoli distal to the occlusion. It would appear, however, that the virus reaches the air cells before the occlusion of the finer air passages, where it gives rise to an inflammatory reaction that is essentially mononuclear, and at the same time causes either a proliferative or a regenerative response on the part of the respiratory epithelium. The considerable number of mitoses present in the enlarged epithelial cells indicates an active process. This reaction is an extremely unusual one in connection with acute inflammations of the lung, and is the only distinctive microscopic change found in this case. The essentially mononuclear character of the exudate suggests a milder, non-destructive type of irritant action, and this point is borne out by the evident stimulation of the epithelial lining of the alveoli. The most intense reaction falls short of that in a typical acute pneumonia. Fibrin is scanty and mononuclear phagocytes predominate in the exudate. Interstitial pneumonia is practically lacking in the present case, the lymphatics showing only the widen-

ing associated with oedema. Only one instance of thrombosis of a small vessel was encountered in many sections from all parts of the lungs. It is quite possible that a secondary infection may explain the fibrino-purulent character of the most active inflammation, and possibly also the fatal termination. Gram-Weigert stains on the tissue showed a few bacterial forms suggestive of pneumococci.

### CONCLUSIONS

- 1 Three cases of psittacosis are described clinically with autopsy findings in one case
- 2 The clinical picture may be one of atypical pneumonia or of a typhoidal state. The mortality occurs in the former, especially in older individuals
- 3 The pneumonia is of the bronchial type with collapse of lung and the exudate is chiefly of phagocytic mononuclear cells
- 4 The most distinctive feature in the pneumonia is an hypertrophy and hyperplasia of the epithelial cells lining the alveoli. However, these cells do not enter into the formation of the exudate
- 5 The most recent work would indicate that psittacosis is caused by a filterable virus
- 6 At the present time a diagnosis of psittacosis cannot be made without establishing contact, direct or indirect with a parrot or other tropical bird

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# A Committee on Applied Medical Science

By JAMES M. ANDERS, M.D., M.A.C.P.

THE writer feels strongly that fresh discoveries of greater or less importance fail of being utilized in a practical manner as promptly as they should be, so that our scientific achievements have ever outstripped our practical performances in the past. He has in previous articles dwelt upon the fact that popularization of science has been lagging too far behind the march of scientific advances, and urged the need of measures or practical means to facilitate the serious application of important fresh discoveries. As stated elsewhere by the writer, "It is to the utilization for human progress of established truths, in even greater degree than to pure fundamental research, that college and university students should devote themselves."<sup>1</sup>

The research method of study should include the reasonably prompt application of newly discovered facts. It should be the function of the university and college to follow the original achievements of the laboratory with prudent attempts to insure their prompt application as far as possible for the benefit of mankind. Too often, then, well proven scientific discoveries fail to be translated into human uses until after a long period of delay. For example, when nitrous oxide was first produced it was known,

and used only, as "laughing gas", but now, many years later, it is being used extensively by both the dentist and the surgeon as an anesthetic.

Again, ether as an anesthetic was discovered long ago—some 300 years—before it came into common usage to relieve the pains occasioned by surgical procedures. More especially in recent times, during which the discoveries of science have shown a great numerical increase, has the human race failed to receive the benefits of which they are capable, as quickly as has seemed possible and desirable.

The use of diphtheria toxin-antitoxin was first suggested by Dr. Theobald Smith to prevent diphtheria, in 1907, and in 1913 von Behring demonstrated its safety when employed as a prophylactic among young babes against that dreaded disease. It was not, however, until more than ten years later that a serious effort on the part principally of public health officials, was made to immunize children against diphtheria. It is not known definitely what percentage of childhood in the susceptible period has been protected to date, but it is doubtless less than fifty per cent. Who will compute the loss to humanity in lives alone from such unreasonable and unjustifiable delay?

True it is, that during the last three decades there was available diphtheria antitoxin for the treatment of this affection and by this specific means the mortality rate has been kept as low as ten per cent. Moreover, it is to be recollected that if this remedy had been administered early, and in proper dosage in all cases, there would be practically no mortality. It has not seemed possible to accomplish this, however, hence the necessity of administering universally the toxin-antitoxin if we would hope to eradicate this disease. It was confidently predicted a few years since, by certain leading public health workers, that in the course of five years diphtheria would be exterminated in some quarters, at least. And this prediction would have come true, had public opinion been sufficiently aroused, or enthusiastically and universally favor-

bestow exclusive attention to the field of preventive medicine.

Many scientific advances outside of the field of medicine have met the same fate. To illustrate, gunpowder was used for amusement by the Chinese centuries before Europeans put it to its present day uses. The Wright brothers learned how to fly by using the airplane as a glider. As pointed out by Slosson, however, "aviation would have remained for a generation or so in the class of amateur sports, but the war forced it pre-maturely into maturity, possibly not to the advantage of its development." Another illustration may be cited, it is known that the steam engine was a mere plaything in ancient Alexandria, but some seventeen hundred years later, Watt converted it into a working machine.

Again, the comforts and conveniences of modern life are to be credit-

make full use of it. What such a person needs is to acquaint himself with the simple elementary yet well established facts and laws appertaining to the physical sciences and then promptly apply them to his daily life and habits. Even among the cultured classes the fundamental laws of health are frequently overlooked. It is another instance of failure to make proper use of established scientific truths.

It is not always the most important laws, that are first fully applied to daily living. To determine the cause of the frequent delay, however, is a puzzling question. Once a verified, safe preventive for a dreaded infectious disease is found, it would seem that its universal, intelligent use must follow promptly and the disease be eradicated, but such is not the case as has been shown above by convincing data concerning diphtheria. It is true, on the other hand, that the prompt application of specific means of prevention in infectious diseases would confer the greatest benefit upon mankind. Here may be mentioned the fact that while modern medicine has protected the human race against some of the most devastating infections,—for example, smallpox, typhoid fever, cholera, tuberculosis, typhus fever, yellow fever (in America) and others, there has not been the active co-operation on the part of the organized medical profession and intelligent laity in that progress, more especially in the matter of the practical application of the scientific discoveries which made it possible, that could have been desired.

One of the principal purposes of this paper is to direct attention to the

importance of promptly putting into effect, more especially, such positive advances as are emanating from the laboratory, and have a bearing upon human health and welfare. Care should obviously be taken to avoid precipitancy, which would compel a too frequent reversal of attitude toward these advances.

The suggestion is advanced here, that a council of experts be appointed by a nationally organized medical body such as the American College of Physicians. Such a council or committee could determine the practical significance of new scientific discoveries in hygiene, medicine and preventive medicine, and could also create an enlightened public sentiment with regard to those calculated to promote human welfare by new, though well established means and methods. It is clear to the writer that such a medical council or committee, if carefully selected, would be powerful in hastening the utilization of useful and life saving measures based on verified laboratory results.

The manner of collecting reliable data and the best method of rendering it understandable to the general public are details of importance, it is true, but cannot be discussed here. Suffice to add that experts such as would most probably be selected to make up the council already know where this is to be found and its purport. The council, made up of expert clinicians, pathologists and bacteriologists, would be naturally expected to make a report annually to the American College of Physicians in addition to its work of public illumination and education and to publish

the results of its deliberations during the intervals between the meetings of the College as occasion might seem to demand. The writer feels that its voice would be welcomed and heeded by the general profession.

Such a body of experts would vigorously attack the problem of diffusion of established knowledge not only regarding the causes and approved methods of preventing the communicable diseases, but also those chronic degenerative affections which are taking an increased toll of human beings, it would stimulate the members of the medical profession to greater personal efforts to educate public opinion,—a step so necessary to progress in disease prevention.

The institution known as Science Service at Washington, and headed by the eminent scientist, Edwin E. Slosson, is doing much to popularize scientific knowledge in this country. It, however, does not stress subjects, hygienic and medical, sufficiently, and to obtain the best results we must go to experts in these well-defined fields, and gain their active organized cooperation in some such way as outlined above. In this manner, and in this manner only, can the many aspects of scientific inquiry, as related to dis-

ease and its prevention, be interpreted promptly to the general public and the profession. Steps might be taken by the committee of experts, here suggested, to co-operate with the Science Service above referred to, as well as other agencies, and in this manner the service to humanity be broadened and rendered more effective.

Surely, discoveries that have rendered fatal diseases obedient to our control should be interpreted correctly by the medical profession to the humblest citizen. It seems to me, it is time to overhaul our ideals so that greater efforts will be expended in enlightening the people through the medical profession about the scientific advances which promote human health and happiness, and to a like extent, material progress. To accomplish this objective within a reasonable length of time will prove a difficult undertaking, but since there is urgent need for it, effective ways and means should be found. The method advanced above would provide another opportunity for the organized medical profession of America to extend its influence and increase its usefulness to mankind.

<sup>1</sup>General Magazine and Historical Chronicle July, 1929, p. 479

# Healing of Tuberculosis\*

By F M POTTENGER, M D, *Momona, California*

WE are able to estimate the value of therapeutic measures as applied to any disease in proportion to our understanding of the manner in which the body naturally combats such disease

Infectious diseases, as they affect different people, produce a varying picture. While the same disease is always produced by the same microorganism, yet identical conditions whether in pathology, symptomology or in ultimate results will never be found.

Grant that all human beings would react toward a given microorganism in the same general manner, variations in the disease picture would still occur because of the differences in virulence and differences in numbers in the causative microorganisms, on the other hand, grant that dosage and virulence in infectious microorganisms were always the same they would meet varying conditions of tissue response in different individuals and in the same individual at different times, which would likewise produce disease pictures of great variation.

Applying the above principles to tuberculosis we shall see that the tu-

bercle bacillus acting upon different individuals produces disease pictures of great variety, which are combatted with different degrees of effectiveness.

## *Principles Underlying Healing of Tuberculosis*

Regardless of variations in the disease and differences in the outcome of tuberculous infections, the body carries out its program of protection along certain definite lines, the nature of which we may inquire into with profit. The defense in tuberculosis seems to be largely cellular, yet we can not deny that a certain amount of humoral defense is likewise brought to bear against the invaders (McCutcheon, Strumia, Mudd and others,<sup>1</sup> and Opie.<sup>2</sup>

The program of defense differs according to whether it is a first or a succeeding infection. The former is opposed at first by only the natural defense of the host and later by a developing specific defense; the latter by both natural and specific defense from the start.

Inasmuch as the host shows evidence of immunity in from five or six days to two or three weeks after infection has taken place and since no symptoms appear until the immunity mechanism has been called into

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\*Read before the Fourteenth Annual Clinical Session of the American College of Physicians, Minneapolis, February 10-14, 1930.



action, in our study of clinical tuberculosis we are always dealing with infection in the immune, so the specific factors in defense are always present and upon the degree of their competence depends largely the nature, the course, and the outcome of the disease

Healing in tuberculosis in the immune or adult type, as we speak of it, is accomplished through several different processes, among which are (1) destruction of bacilli, (2) retardation of the passage of bacilli through the tissues, (3) elimination of bacilli through natural channels by caseation and cavity formation, (4) development of a state of desensitization to bacillary and other toxins (5) encapsulation or rendering inactive, viable bacilli which remain in the tissues; (6) ridding the body of the inflammatory products which accompany the infection, and, (7) repair of the injury inflicted upon the body by the disease

In studying tuberculosis as we meet it day by day in the clinic, we get the impression that *healing depends upon the controlling of the size and the effects of the reinoculations and keeping them within the range of the individual's powers to cope with them*. To this end the acquired bactericidal action of immune tissues, the retarding influence of the allergic inflammation upon the passage of bacilli through the tissues, and the desensitization of the host to toxic substances, are probably the major contributing factors. Many otherwise large and dangerous reinoculations are thus rendered ineffective and eventually outcome

*Destruction of Bacilli* To what extent destruction of bacilli takes place in the course of healing of a tuberculous process, and how important this factor is in cure has never been satisfactorily established by experiment Kraus and Hofer<sup>3</sup> reported that they observed destructive effects upon bacilli within an hour after they had been introduced into the peritoneal cavity Wolff-Eisner<sup>4</sup> speaks of a lytic action upon the bacillus which takes place within the body. Certain humoral effects have been shown by the presence of antibodies in the blood by numerous observers, but most observers have considered them as being of secondary importance, when compared with the cellular response of the host The action of phagocytes was established by Metschnikoff<sup>5</sup>, and Wright<sup>6</sup> showed the effects of opsonins in preparing the bacilli for phagocytosis

Recently new data bearing upon the subject has been brought forth Rich<sup>7</sup> believes, although he offers no direct proof, that destruction of bacilli is a very important mechanism granted to the body by a previous infection Laine<sup>8</sup> reports experiments in which by using one type of bacillus for primary inoculation and another type for reinoculation, he has been able to show that the resulting pathogenesis was due to activity on the part of the bacilli remaining in the tissues from the first infection and that the bacilli of reinoculation were practically all destroyed, without preliminary multiplication

I have for a period that in the more destruction of bacilli takes place with the bodies of phagocytes

ing from clinical tuberculosis. It has seemed to me to be the only way that we can understand the healing of an extensive lesion. Such visible infections as those in the eye, testicle and larynx are of comparatively frequent occurrence in the course of chronic pulmonary tuberculosis, and very often prove to be abortive showing that the bacilli have been destroyed. Other infections which take place from one part of a lung to another, and prove to be only temporary affairs, are frequently noted when patients with advancing lesions are closely watched and frequently examined, and particularly when frequent x-ray plates are taken for comparison. Often such serial x-ray plates show a new focus to appear in a certain part of the lung field, only to clear away after being present for a brief time, say a month or two. The very fact that bacillemia, which is so often present, fails to cause uncontrollable extensions regularly is further proof of the body's destructive action on bacilli.

#### *Retardation of Passage of Bacilli Through the Tissues*

The allergic inflammatory reaction performs what is usually recognized as a special protective service in inhibiting the free passage of bacilli through the tissues. Were it not for this service nothing but a quick and efficient bactericidal action on the part of the body tissues could save any one suffering from advancing tuberculosis from destruction; yet the recovery of such patients is a common observation in clinical practice. Koch's first observed the restraining influence of

allergy and Krause and Willis<sup>10 11</sup> showed the extent of the retardation experimentally. They showed that bacilli are carried from the site of inoculation to the adjacent lymph glands in nonimmune pigs in an hour, but require two weeks in the immune. They make the circuit of the entire body and are found in the organs generally in three or four days in the nonimmune, but require three or four weeks in the immune. Inasmuch as preventing the disease from spreading is a condition necessary to healing it readily can be seen how important and how necessary this property of allergy becomes to the tuberculous host.<sup>12 13</sup>

In normal hosts, bacilli lying in the air passages are quickly picked up by phagocytes and carried through the alveolar and bronchial walls, as has been shown in experimental animals. In advanced tuberculosis, where not a few bacilli at infrequent intervals, but millions of bacilli daily, are found in the air passages under conditions in which phagocytosis is increased, in order to account for the failure of infection to take place we must assume either that the bactericidal power which exists on the part of the immune tissues of the host have attained almost an unbelievable degree of competency, or that the tissues themselves resist the entrance and transport of the bacilli. Rich<sup>7</sup> does not believe that the evidence for the restraint of bacilli from entering and passing through the tissues is sufficient, but believes the real defense, which has been so generally observed from the early experiments of Koch<sup>8</sup> to the present time is due to the destruction of bacilli.

and not to the retardation of their migration in the tissues

Opie,<sup>14,2</sup> on the other hand, has recently reaffirmed his view formerly expressed,<sup>15</sup> to the effect that immune tissues fix foreign protein at the site of injection from which it may be recovered for a period of time, and states that anaphylactic shock is prevented by this local fixation process. While this may not prove that the same thing is true of bacteria, he calls attention to the similarity of behavior of the immune tissues to tuberculin, abortin and other similar bacterial products, and also cites, apparently with approval, the experiments of Cecil and Blake<sup>16</sup> who found that the blood stream of monkeys vaccinated against pneumococci by intratracheal inoculation shows less invasion than the unvaccinated

*The Elimination of Bacilli from the Body by Necrosis and Cavity Formation.* The elimination of bacilli through the natural channels of the body, such as the bronchi, bowel, and urinary tract becomes an important phase of defense in extensive lesions.

In advanced destructive lesions large numbers of bacilli are gotten rid of daily by being ejected from the body through the bronchi, and countless others through the gastrointestinal canal. During the time that these bacilli are within the natural channels of the body, if the patient were not protected by some specific barrier of defense, he would be in danger of their penetrating into the tissues and forming new foci of disease.

The destruction of tissue as it occurs in pulmonary tuberculosis through the breaking down of con-

glomerate tubercle and cavity formation with the discharge of the focal contents into the bronchi to be carried outside of the body must be looked upon as having paradoxical interpretation. The destruction is due to the relatively large numbers of bacilli engaged in the reinoculation at a time when the tissues are markedly sensitive to tuberculo-protein. It would not take place if the infection were produced by a few bacilli only, even if sensitization were marked; but it results because of massive dosage when sensitiveness is marked. It is doubtful whether any host could withstand the disease which would be caused by such quantities of bacilli should they scatter into the tissues, if we may judge by the consequences of ruptured bronchial glands and the resulting caseopneumonic lesions which follow, or of miliary infection following severe bacillemia. So from this standpoint the destructive process is without doubt conservative. Nor could the tissues heal with such masses of bacilli within them. Therefore, unless the host is able to destroy the large numbers of bacilli contained in the caseous masses, the only opportunity for healing must come through their expulsion even though damage be done to the host by the loss of tissue.<sup>1</sup>

*Desensitization of the Patient to Toxins.* While we have no method of measuring the toxins which a patient withstands during the course of pulmonary tuberculosis, it is reasonable to assume that by exposing to a patient a small amount of toxin the disease process may be retarded or even arrested at the beginning of the infection. It is not possible to

vere toxemia with equal or more prostration than will be caused later when the infection has extended and multiplied many fold and increased the amount of toxins enormously

It is undoubtedly one of the results of the action of the patient's own tuberculo-protein that it desensitizes him and prepares him to withstand larger and larger doses of bacillary protein without serious harm. This seems to be a necessary part of the immunity mechanism without which patients with advanced tuberculosis would not be able to endure their disease, let alone having an opportunity of overcoming it (Pottenger<sup>18</sup>). It is also probable that the patient is desensitized to the toxins produced by his own tissues. This is illustrated by the following case

No 9564 Mrs E W Aged 35 years Entered sanatorium May 5, 1929 Important previous history measles at 32—quite severe, appendectomy at 27, operation for acute ileus at 30, influenza at 35, pneumonia at 31, followed by pleurisy for three weeks Excellent health except dry hacking cough up until October 1928, when she developed severe cold followed by persistent cough and expectoration Treated for bronchitis Another severe cold December 1928 Temperature not taken Tuberculosis not suspected During April 1929 patient complained of severe exhaustion, loss of appetite, poor digestion, nausea, eructation of gas, profuse sweats right-sided pleurisy, a loss of fifteen pounds in weight, and severe cough with considerable sputum

The temperature and pulse curves for a period of eight months, and X-ray films taken at intervals during the eight months, are shown in Fig 1 and Fig 2 A, B, C and D On entering the sanatorium patient was too weak to sit up for examination Showed extensive bilateral tuberculosis, caseopneumonic in type, throughout upper half of the left lung, with cavitation and a lesser in-

filtration in the upper third of the right lung, as shown in Fig 2 A Temperature 103-104°, pulse 90-108, as seen in chart, Fig 1 The disease continued to extend and showed increased areas of softening, as indicated in the film Fig 2 B, taken August 30, 1929, which shows entire left lung involved Temperature, however, had become lower, as will be noted in the chart Appetite improved, digestive disturbances lessened, and sweats disappeared Patient felt much better This improvement in symptoms continued through November, although temperature remained high, and as will be seen in the film Fig 2 C, taken October 15, 1929, softening continued to take place throughout the lower portion of the left lung, where several cavities seems to be in process of forming In December patient began to have chills and increased symptoms of prostration drenching sweats, appetite and digestion poor, increase in temperature, and the cavities in the lung were more definite, as shown in film Fig 2 D, taken December 2, 1929 Whether this will continue and cause the death of the patient, or whether after excavating the lower lobe she will improve, remains to be determined \*

I should like to call attention to the disparity between pulse and temperature throughout the course of the disease A relative bradycardia is present, indicating a preponderant action of the vagus in spite of the severe stimulation of the sympathetics caused by the toxemia

In comparing the temperature curve, the symptoms as here recited, and the extent and severity of the lesion as indicated by the plates, it will be seen that the patient had fewer symptoms, and lower temperature, with a severe and more widespread lesion than she had originally, with a more limited lesion In explanation of this, we must assume that it was due to the establishment of a strong immunity to both tuberculo-protein and to whatever protein was derived from the destroyed lung tissue otherwise, there is no explanation of her ability to

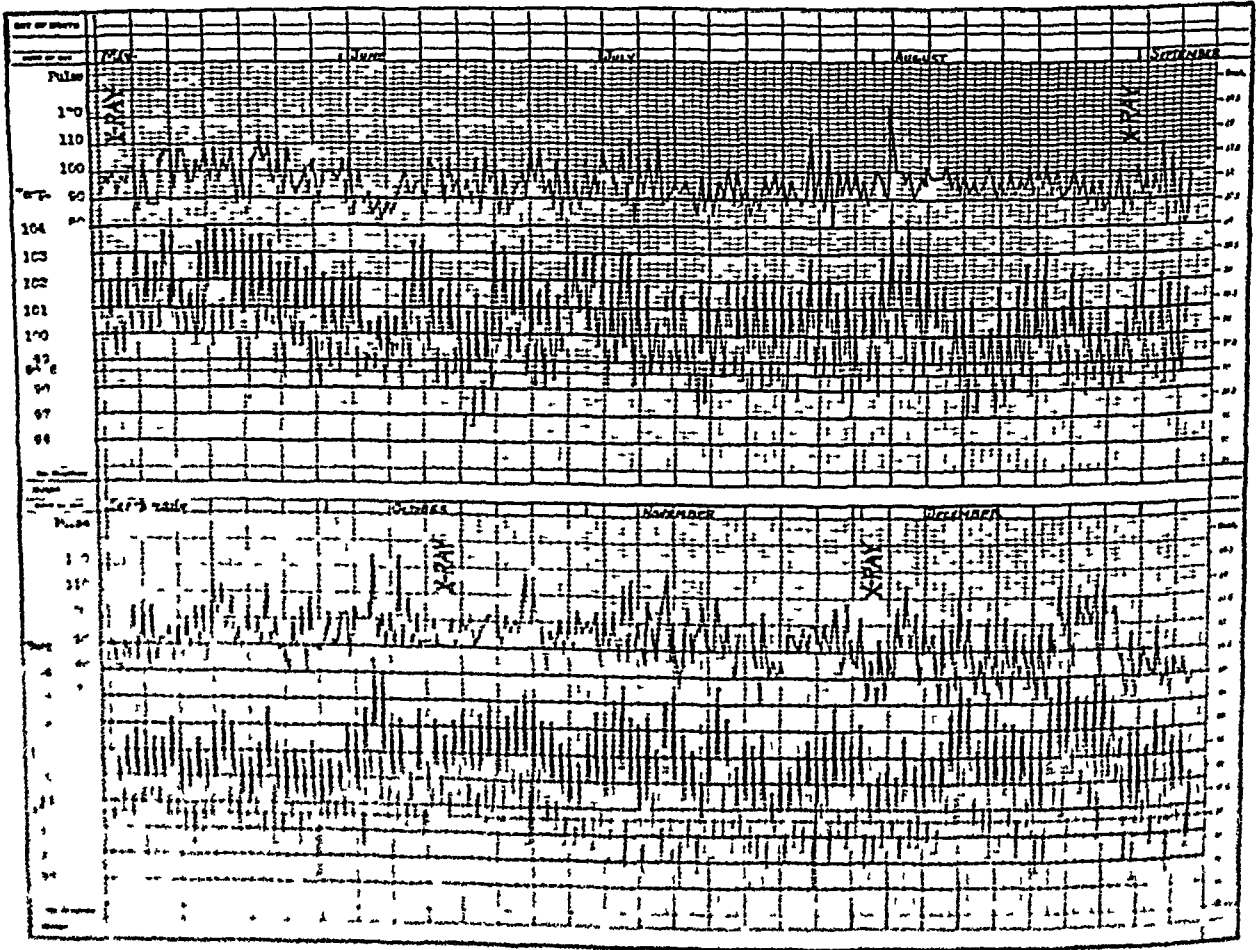
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\*Patient has continued to run the same temperature of 100-101 and maintains same general condition Aug 30 1930

POTTENGER SANATORIUM FOR DISEASES OF THE LUNGS AND THROAT  
MONROVIA, CAL.

TEMPERATURE CHART

MAY-5-1929 to  
DATE SEPTEMBER-5-1929 192- NAME MRS E. W. NO. 9564





Figs. 2 A, B, C and D illustrate an extensive exudative lesion with cavity followed by extension and increased cavitation. The toxic symptoms, however, were much greater at first, with the limited amount of disease shown in Fig. 2 A, than they were later as shown in Fig. 2 A, B, C and D although the disease has extended and cavitation had decreased. The temperature curve is shown by chart Fig. 1.

Fig. 2 A May 6 1929 shows a moderate infiltration in the upper half of left lung with cavity near apex, slight lesion in upper right.





FIG 3 C, October 15 1929, shows softening continued to take place throughout the left lung, where several cavities are in the process of forming





1413 IV  
12-2-29

improve her general physiologic activity while the disease was spreading and showing increased activity pathologically. Desensitization to the patient's own tuberculo-protein, and to whatever other protein was thrown into the system from the broken down lung tissue, is a condition necessary to the understanding of the apparently paradoxical relation between the advancing disease and the lessening of symptoms. Another very interesting thing which suggests the existence of a high degree of specific protection (immunity) is the failure of the disease in the right lung to extend, and a failure of the large quantities of tuberculo-protein which must have been thrown into the blood stream during this time, to cause sufficient reaction to produce marked exudation and caseation in the upper right lung.

*Encapsulation and Rendering Inactive Viable Bacilli* Encapsulation is one method by which the host renders bacilli harmless though remaining within the body. The condition precedent to such a favorable procedure is that the numbers of bacilli be few, so few that they fail to produce sufficient reaction to cause more than a temporary exudation or more than a very slight necrosis. When extensive necrosis, with loss of much tissue, has once taken place then a replacement must be brought about, and this must be preceded by the elimination of most of the bacilli from the caseous focus and the regeneration of the destroyed tissues. So healing under these circumstances is more complicated.

Attention must also be called to the fact which has been pointed out by Bartel,<sup>19</sup> Opie,<sup>20</sup> and others that bacilli may remain in the tissues maintained in a viable though inactive state, for long periods of time. This must be due to another phase of spe-

cific defense though as yet there seems no adequate explanation for it.

*The Elimination of Products of Inflammation* Exudation of some degree is the part of every active tuberculous process. Healing can not be said to have taken place until all exudative phenomena have disappeared. According to the severity of the lesion, exudation may mean only a slight hyperemia, or it may mean the pouring out of serum, cells and fibrin in the tissue. In clearing the field for healing it is necessary to have all such products rendered absorbable or in a condition to be dealt with by the phagocytes. Purely exudative phenomena accompanying tuberculosis clear away by resolution, the same as occurs in acute pneumonia, except a much longer time is required. Should irritation reach a certain degree, however, when resolution has been completed, changes of a proliferative type will be necessary to complete the healing process.

*The Repair of Injury Done* If the lesion is caused by only a few bacilli, the destruction of tissue is negligible and healing is a comparatively simple process. If the lesion is a slowly advancing one, and caused by the repetition of many small inoculations, the necessary amount of injury may be brought about to disturb the patient's physiologic activity before sufficient specific resistance has been engendered to overcome the infection, and still there be a minimum of tissue loss.

Lesions produced by many bacilli or bacilli of high virulence in patients with highly sensitized cells, on the other hand, create conditions which

are markedly inflammatory and often destructive in character from the very beginning, and require a complicated program of resolution and tissue regeneration to repair the damage which has been done. Bacilli and the various inflammatory elements are subjected to enzyme action, and phagocytosis until the field is relieved of all abnormal debris, and then if destruction has taken place, repair follows the usual pathological course of regeneration, being modified of course by the fact that healing must often be accomplished while viable bacilli remain embedded in the tissues. Even cavities of considerable size may be healed at times with a regeneration of tissue.

*How Therapeutic Measures Aid the Process of Healing*

Rest is not the ideal status of any individual for a prolonged period of time, but in tuberculosis it is a matter of necessity.<sup>21</sup> The eight or nine hours of daily rest which is capable of maintaining the physiologic balance of the body cells in states of health is wholly inadequate in tuberculosis. In the treatment of tuberculosis we often find it necessary to maintain rest for the entire twenty-four hours for long periods of time—sometimes for many months—because we have a departure from the normal status of such a nature that exercise during the stage of active disease favors extension of infection, increase of toxemia, and lowers resistance, causing the patient's body functions to be carried on at a low standard of efficiency. These factors interfere with healing.

also vitamins and salts in ample amounts is necessary to the best progress against tuberculosis. The Sauerbruch<sup>22 23 24</sup> diet has seemed to be of decided advantage in tuberculosis of the skin, but, so far, not much has been claimed for it in diseases of the pulmonary form. But it has long been recognized that the patient who is a poor eater and unable to take a well balanced diet rarely makes a satisfactory progress in the healing of tuberculosis.

From the discussion above it is clear that it is the mild infections which disturb the patient least and are easiest to overcome, and that it is the severe ones which are dangerous. Larger infections are more dangerous to the patient because they cause more acute inflammatory and destructive reactions, multiply the foci from which extensions may take place, and increase the toxemia which the patient is obliged to combat.

Anything that will increase the likelihood of the disease extending or of carrying the tissue reaction beyond the limits of safety are prejudicial to recovery. On the other hand, anything that will decrease the number of extensions, tend to hold their severity to a low limit, and make the patient more tolerant of toxins and stimulate perifocal fibrosis, will aid recovery.

In the final analysis the patient if healed at all, is healed by his immunity mechanism. The effect of the patient's own reinoculations of bacilli or bacillary protein are helpful in promoting healing unless they are too severe; but if very severe they may be harmful, but that he could not attain the necessary immunity to heal without

them must be evident to all careful students of the immunological reactions in tuberculosis. It is his reinoculations that, acting on his sensitized cells, cause the allergic inflammatory reactions which result in restraining the passage of bacilli through his tissues, in stimulating the bactericidal properties of the tissues, in desensitizing the patient to the poisonous proteins, and in stimulating the perifocal cells to the formation of fibrous tissue. Whether the patient wills it or not, he is treated and aided in cure by his own tuberculin, as has been stated by Long,<sup>25</sup> and retarded in healing only if the dosage be exceeding large. Therefore, the necessity of tuberculo-protein reinoculations is obvious, but the necessity of keeping them within bounds is equally obvious.

The following cases, whose clinical progress may be judged from the plates and the appended charts, illustrate the principles discussed in the preceding pages.

The plates shown in Figs 3 and 4 both represent limited apical lesions, one of which healed promptly under the usual sanatorium regime, the other only after compression therapy had been employed. The difference in time of healing in these two patients was probably due to differences in their respective resistance, which probably means differences in the physiochemical reaction of their body cells. There is no evidence of virulent infection in either case, neither is there evidence of spread aside from that noted in Fig 2 C, but there is a great difference in the time of healing, the case represented by Fig 3 requiring a year, and that represented by Fig 4



FIGS 3 A and B illustrate healing of early infiltration with almost complete resolution  
FIG 3 A, June 26, 1928, shows moderate infiltration of the upper half of left lung and apex of right lung

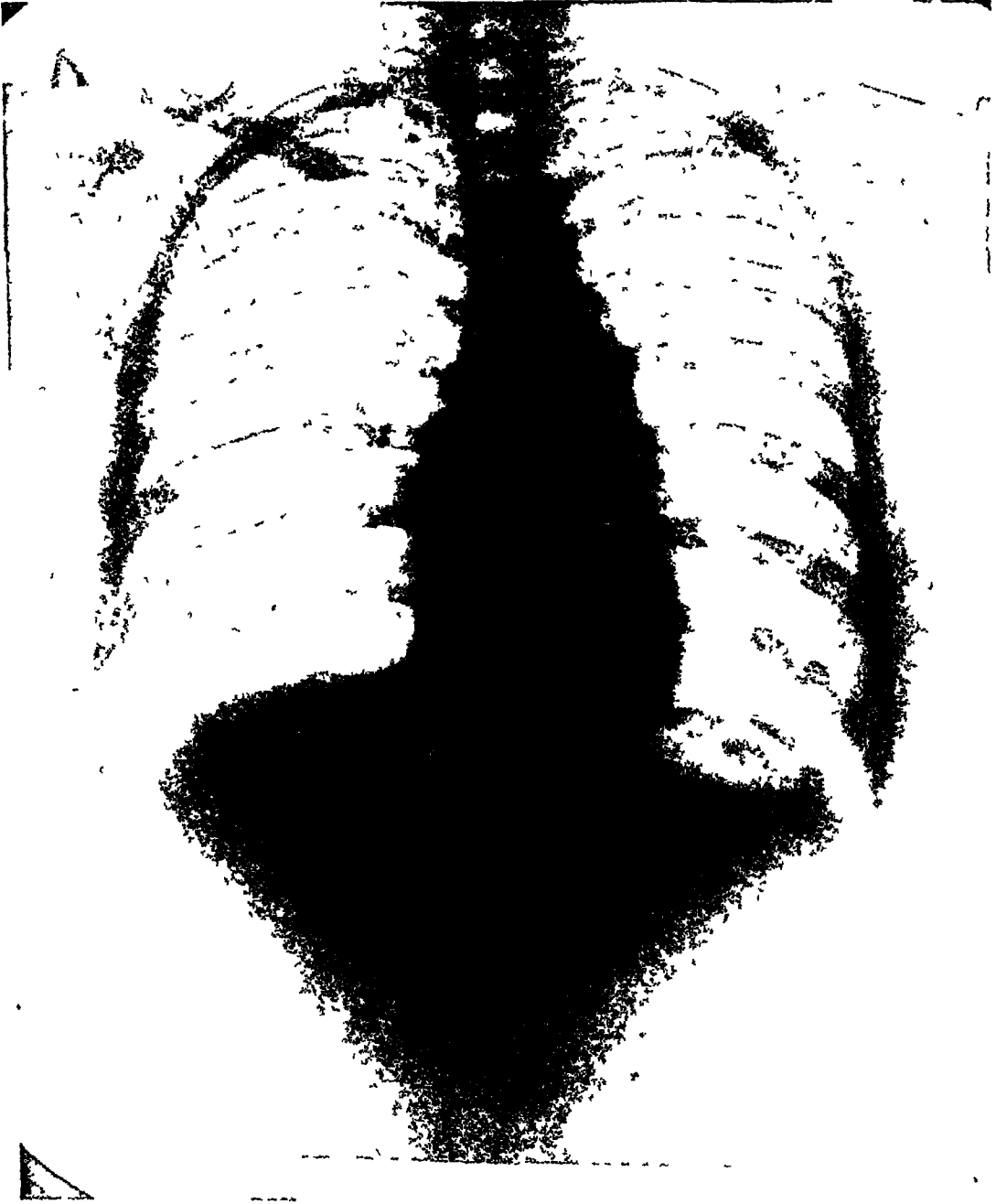


FIG. 3 B, January 10, 1930, eighteen months later, shows almost complete disappearance of lesion

requiring three and one-half years to complete the healing.

*Case No 9026.* Miss A. C. Fig. 3 A and B, are films of a patient with an early tuberculosis involvement of both apices. She came under my care June 26, 1928. Film A shows the involvement at the beginning of treatment. Film B, taken January 10, 1930, shows how completely the lung had cleared. This patient was under treatment from June 26, 1928 until August 23, 1929. She had been away from the sanatorium four and one-half months, when film B was taken.

*Case No 9481.* Mr E. P. Fig. 4 A, B, C, and D, are films of a patient with slight involvement of the left apex, who came under my observation May 17, 1926. Film A shows involvement at beginning of treatment. He had not been able to clear the lung in fourteen months' time, as will be shown in film B, taken July 13, 1927. Two months later, as will be seen in film C, the disease had extended very markedly. An exudative lesion is seen through the upper half of the left lung. On account of the apparent lack of resistance on the part of the patient, we considered it necessary to institute artificial pneumothorax, which resulted in a healing, as shown in film D, taken November 12, 1929.

Figs 5 and 6 represent tuberculosis with acute onset in which cavity was formed very shortly after the first symptoms appeared. Cases such as these have been recently described by Redeker. He recommends that they be treated by the immediate institution of pneumothorax, because he believes that otherwise they will usually fail to heal. We have found, on the contrary, that these lesions usually heal satisfactorily by rest and the regular sanatorium regime, provided treatment is started at once. The healing is by resolution and a mild degree of fibrosis, except in case of the cavity which requires the formation of considerable

fibrous tissue. The cavity that heals best is the fresh cavity without too much fibrous tissue about it. Immediate treatment is essential to the successful handling of these cases.

*Case No 9388.* Miss R. M. Fig. 5 A, B, and C, are films of a patient with acute onset in which the process was preponderantly exudative in type, with cavity formation within three weeks after the onset of clinical symptoms. The patient was apparently in perfect health when she was taken ill with influenza on Thanksgiving day, 1928. She was examined by me in less than three weeks following the onset of influenza, and gave the picture as shown in Fig. 3 A, taken December 18, 1928. This process, under rest and other sanatorium measures went on to a satisfactory healing, the progress of which is shown in film B, taken August 8, 1929, and film C, taken January 1930.

*Case No 9679.* Miss G. M. Fig. 6 A and B, represents a similar acute process. Patient gives history of dieting for overweight until August 7, 1929, when she had two teeth removed and failed to regain her usual health thereafter. In September she noticed a cough with expectoration, and a temperature of 101°, and severe pain over the right lung. On October 13, the film shown in Fig. 4 A was taken, in which there is an extensive right-sided involvement, with definite cavity formation.

Patient was put on rest and given the usual sanatorium treatment. She had a temperature of 101° for about a month, when it subsided, and with its subsidence the cough and sputum disappeared. Film B, taken on January 13, 1930, shows that the cavity has disappeared. This patient is not yet well, but is rapidly recovering\*.

We also see the tendency to heal in many cases which are of longer standing, even though temperature has persisted for a considerable time. The determining factor seems to be the way the patient's physiologic balance is re-

\*Aug 10, 1930 cavity healed



FIG. 3 A, B, C, and D show an early apical lesion which failed to heal under ordinary hygienic regimen but, on the contrary, the disease extended and was healed only after pneumothorax was instituted.

FIG. 4 A taken May 17, 1926 shows limited lesion of both apices, more marked on the left.





FIG 4 B, July 13, 1927, twelve months later, shows left apex improved but still unhealed

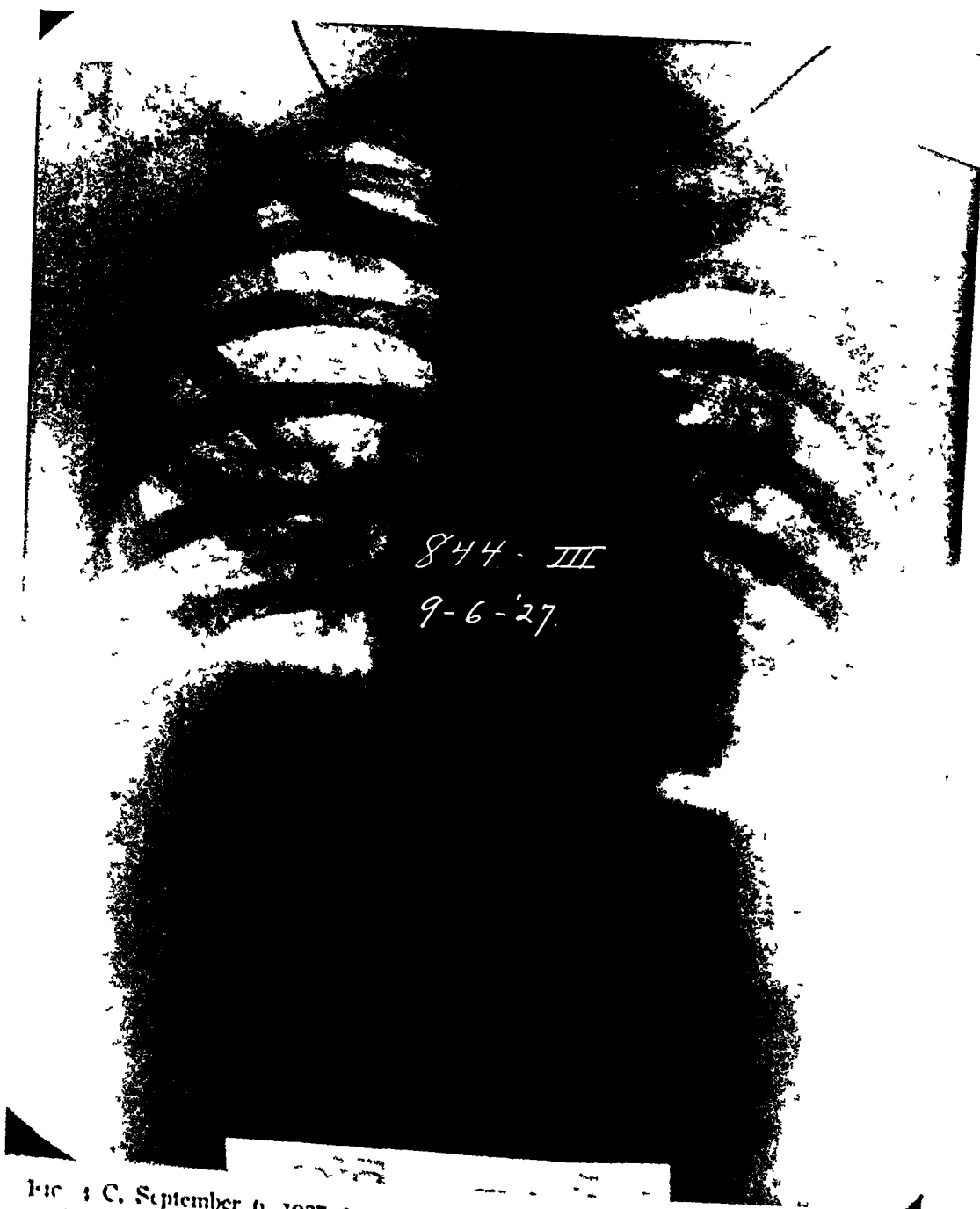


FIG. 4 C. September 6, 1927, two months later, shows extension of the disease in left lung. Owing to apparent lack of resistance on part of patient the lung was collapsed.



FIG 4 D, November 12, 1929, shows apex fairly clear, but lung still unexpanded Patient symptom free



FIGS 5 A, B and C represent an early exudative lesion with rapid cavity formation which healed under regular sanatorium regime, without mechanical interference. Three weeks before onset of symptoms patient was attending High School. An attack of influenza was accountable for the acute onset of tuberculosis. Sputum became negative.

FIG 5A, December 16, 1928 shows acute exudative infiltration in the upper third of right lung with cavity formation.

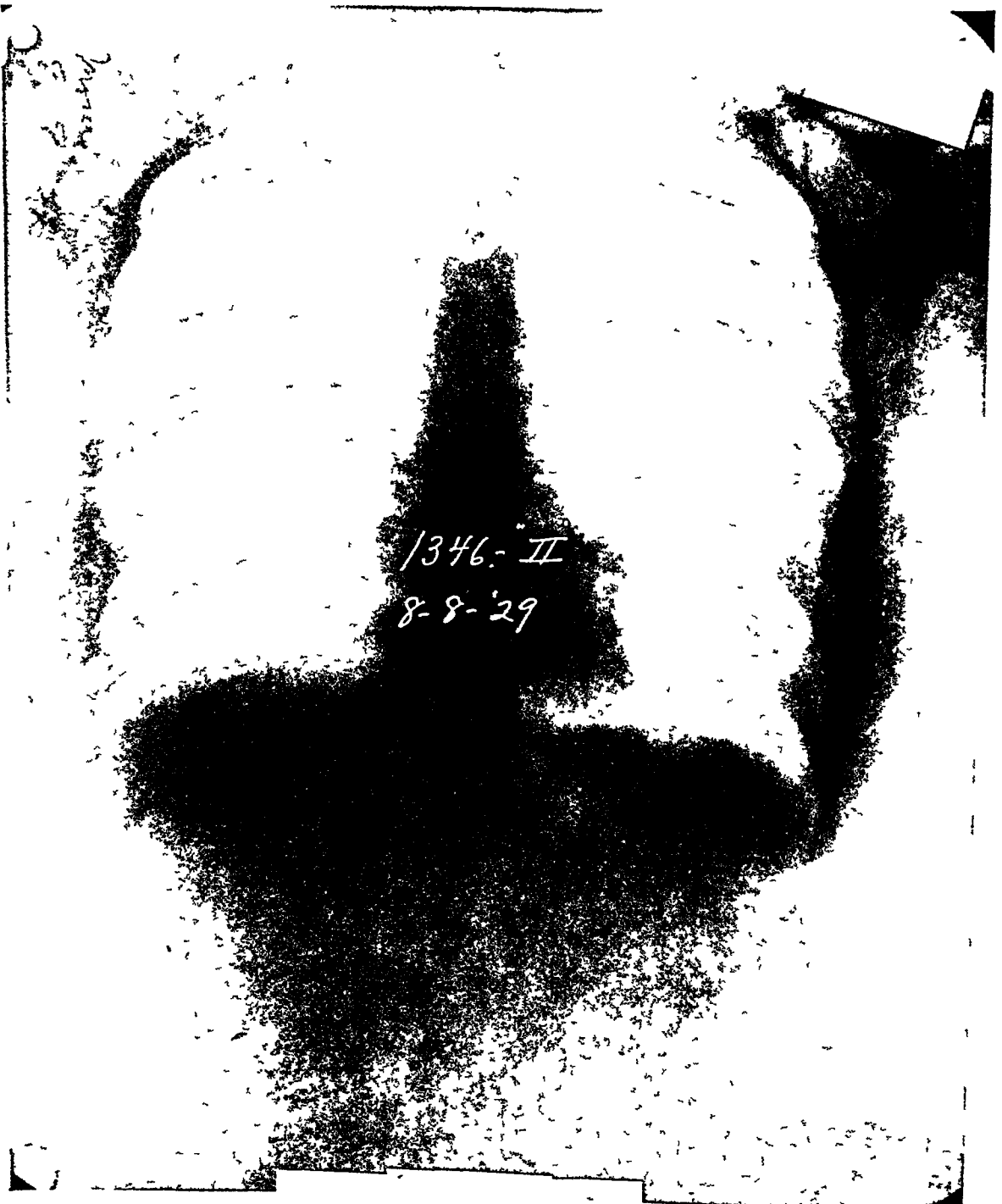


FIG 5 B, August 8, 1929, shows cavity healing

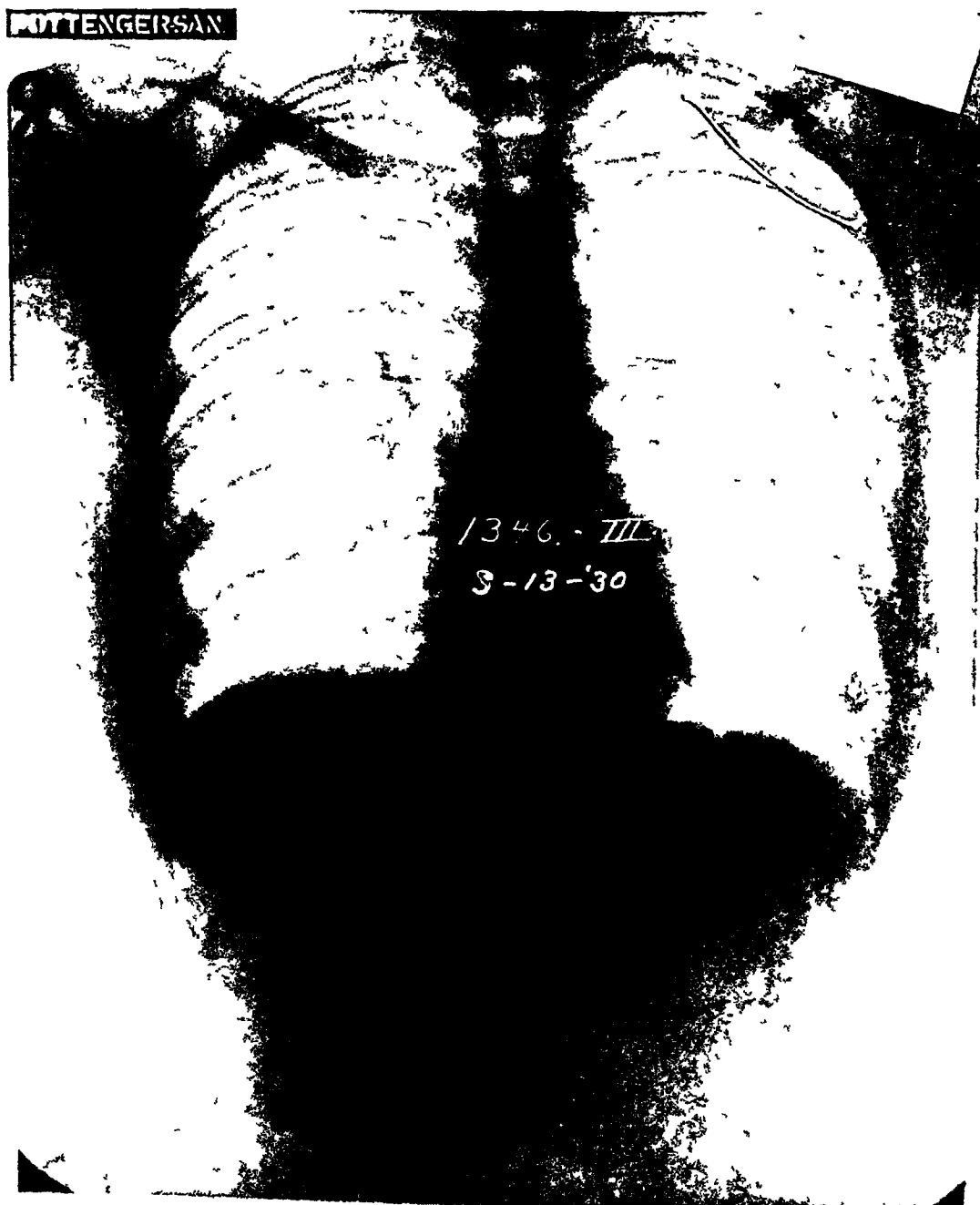


FIG. 5 C, March 13, 1930, shows cavity healed



FIG 6 illustrates the healing of acute exudative tuberculosis with subclavicular cavity, under regular sanatorium regimen, without mechanical interference of any kind Sputum became negative

FIG 6 A, October 14, 1929, shows very extensive infiltration of the upper half of right lung, with cavity

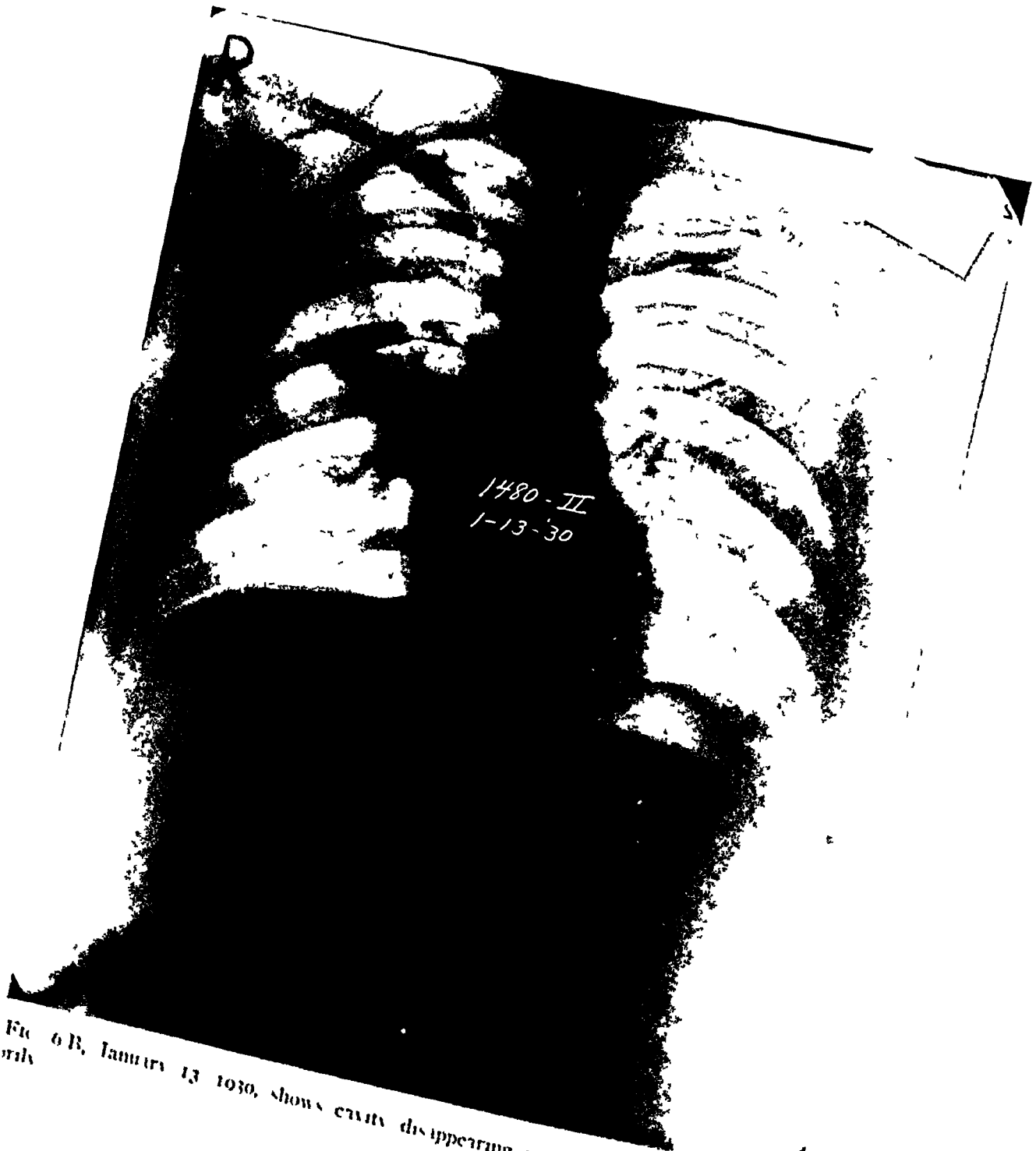


FIG. 6 B, January 13 1930, shows cavity disappearing and healing progressing satisfactorily.



stored, together with the degree of specific defense that he is able to establish

*Case No 9395* Mr S. II Fig 7 A, B, C, and D, illustrates an advanced combined proliferative and exudative lesion with excavation. The patient entered the sanatorium on December 28, 1928. He had been treated by me for an early tuberculosis occupying the upper portion of the right lung, some six years before, and had made a recovery. In July 1928 he had an acute respiratory infection, accompanied by high temperature, which was diagnosed as influenza. Recovery was slow. After recovery from the influenza he again had a rise of temperature accompanied by a persistent cough and expectoration. Failing to make satisfactory improvement he was sent to the sanatorium, with the condition as shown in film A. There are several areas of loss of tissue in the upper half of the right lung. In his temperature chart, shown in Fig 8, it will be noticed that during the first six months he had considerable elevation of temperature. Film B, taken February 8, 1929, shows a slight increase in the exudative character of the lesion, but no increase in destruction of tissue. Film C, taken May 10, 1929, shows a very marked increase in the exudative type of the lesion, but a general improvement in the areas of involvement in the second and third interspaces. These changes had taken place during a course of continuous temperature, which we assume accompanied repeated reinoculations of bacilli and bacillary protein, as will be seen in Fig 8. Shortly after this all appreciable reinoculations ceased, the temperature came to normal, the tuberculous inflammation proceeded to heal by resolution and fibrosis. Film D, taken January 22, 1930, shows the extent to which the right lung has cleared to date.

The clinical improvement in this case was exceptionally gratifying. Upon entering the sanatorium his sputum was 160 cc in 24 hours, with 250 tubercle bacilli per microscopic field. At the time film B was taken, it was

150 cc in 24 hours, with 100 tubercle bacilli per microscopic field. When film C was taken it had dropped to 65 cc in 24 hours, with 6 tubercle bacilli per microscopic field. When film D was taken it was 2 cc in 24 hours, with 30 tubercle bacilli per microscopic field. While the lesion is not quite healed, yet it is rapidly approaching that state. This shows that a far advanced destructive lesion can be turned to a favorable ending, provided co-operation can be had for a sufficient length of time.\*

Patients who show a preponderantly exudative reaction are usually considered as belonging to a more serious group, but they too will often heal even though the disease is widespread.

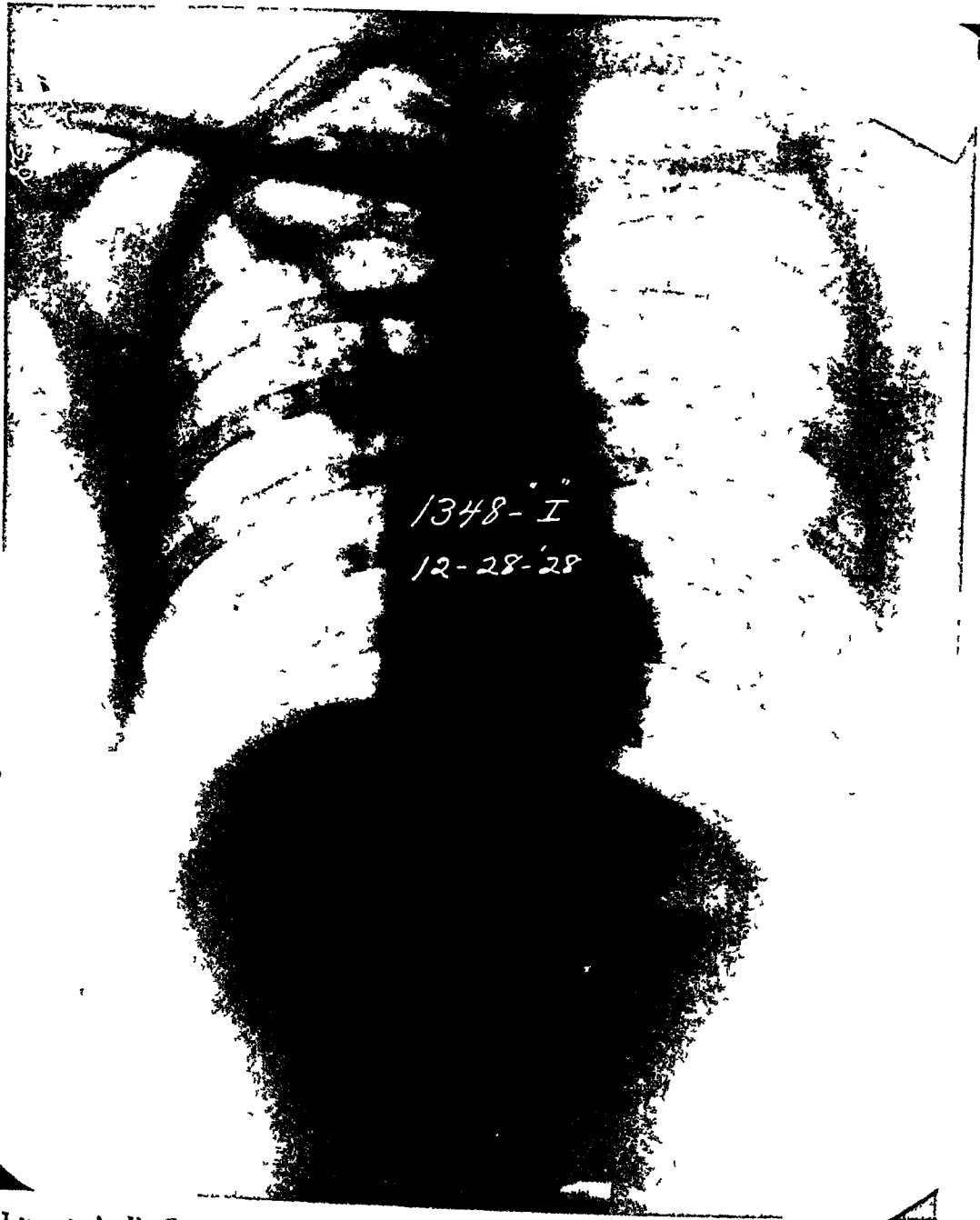
*Case 7670* Mrs W J Fig 9 A and B, illustrates an extensive fibrocaseous tuberculosis, with marked allergic reaction causing a severe exudative process. The patient had been ill for more than a year, had lost weight to eighty-five pounds, and had had fever for several months. On entering the sanatorium (Fig 9, film A) she had a temperature of 101°. The sputum shows 30 cc in 24 hours, with 100 tubercle bacilli per microscopic field.

The patient was under the usual sanatorium treatment. On May 9, 1927, eighteen months later, the lung fields had practically cleared, as shown in film B. At that time she was free from cough, expectoration and tubercle bacilli, and weighed 105 pounds. The case illustrates the natural healing of an extensive lesion largely by resolution.

In cases where a satisfactory physiologic balance can not be restored and immunity can not be built up, the disease will spread in spite of all that can be done. Such patients suffer severe

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\*Aug 10, 1930 Now healed and bacillus free



FIGS 7 A, B, C, and D illustrate healing of extensive combined proliferative and exudative tuberculosis, with cavity formation under regular sanatorium regimen without mechanical interference. The temperature pulse and weight of this patient are shown in Fig 8.

FIG 7 A December 28 1928 shows marked involvement of upper two-thirds of right lung, slight involvement in left, multiple cavitation in right.

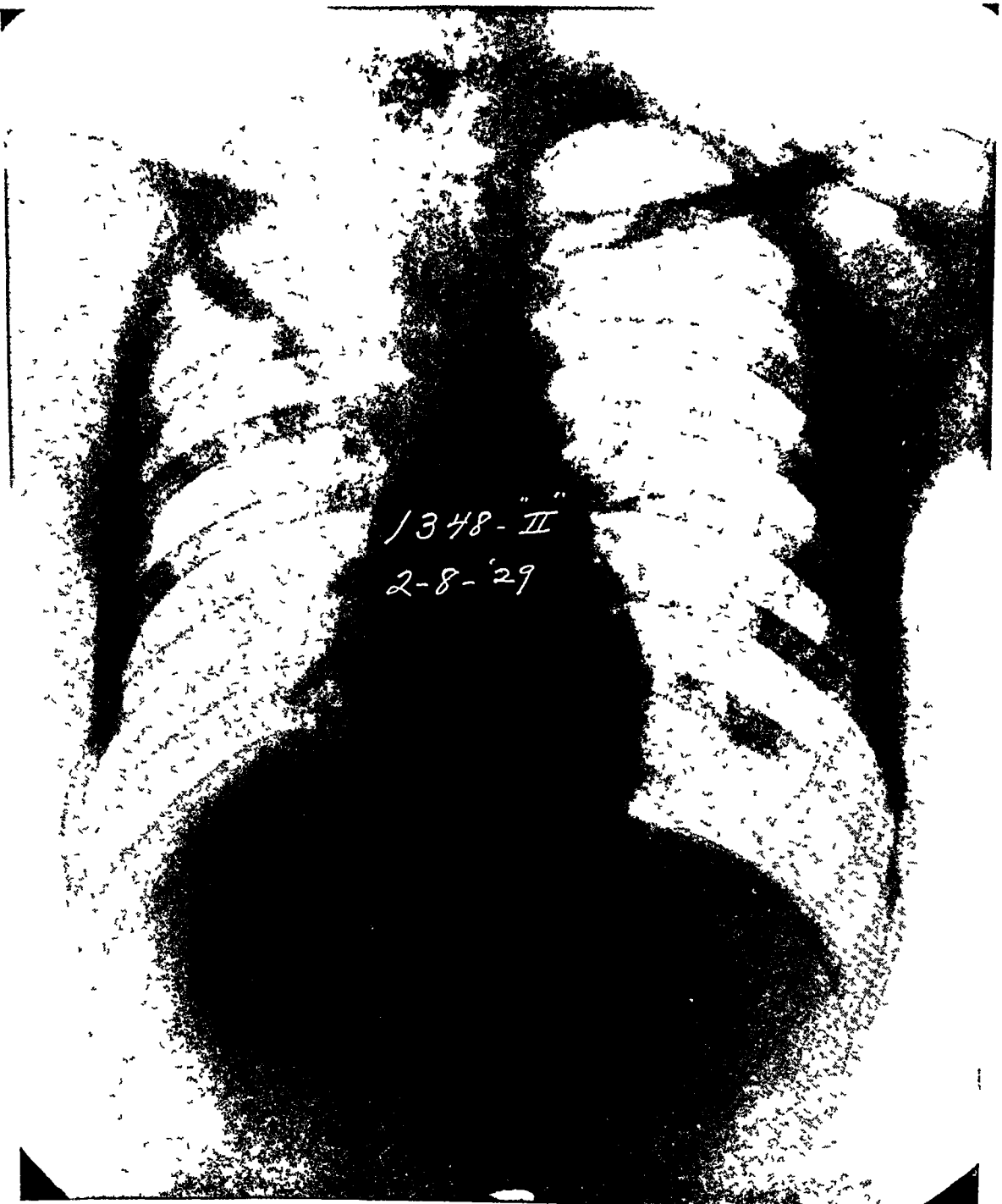


FIG 7 B, February 8, 1929, shows extension of the disease in lower right lung and also in central portion of left lung. At this time an unsuccessful attempt was made to collapse lung.

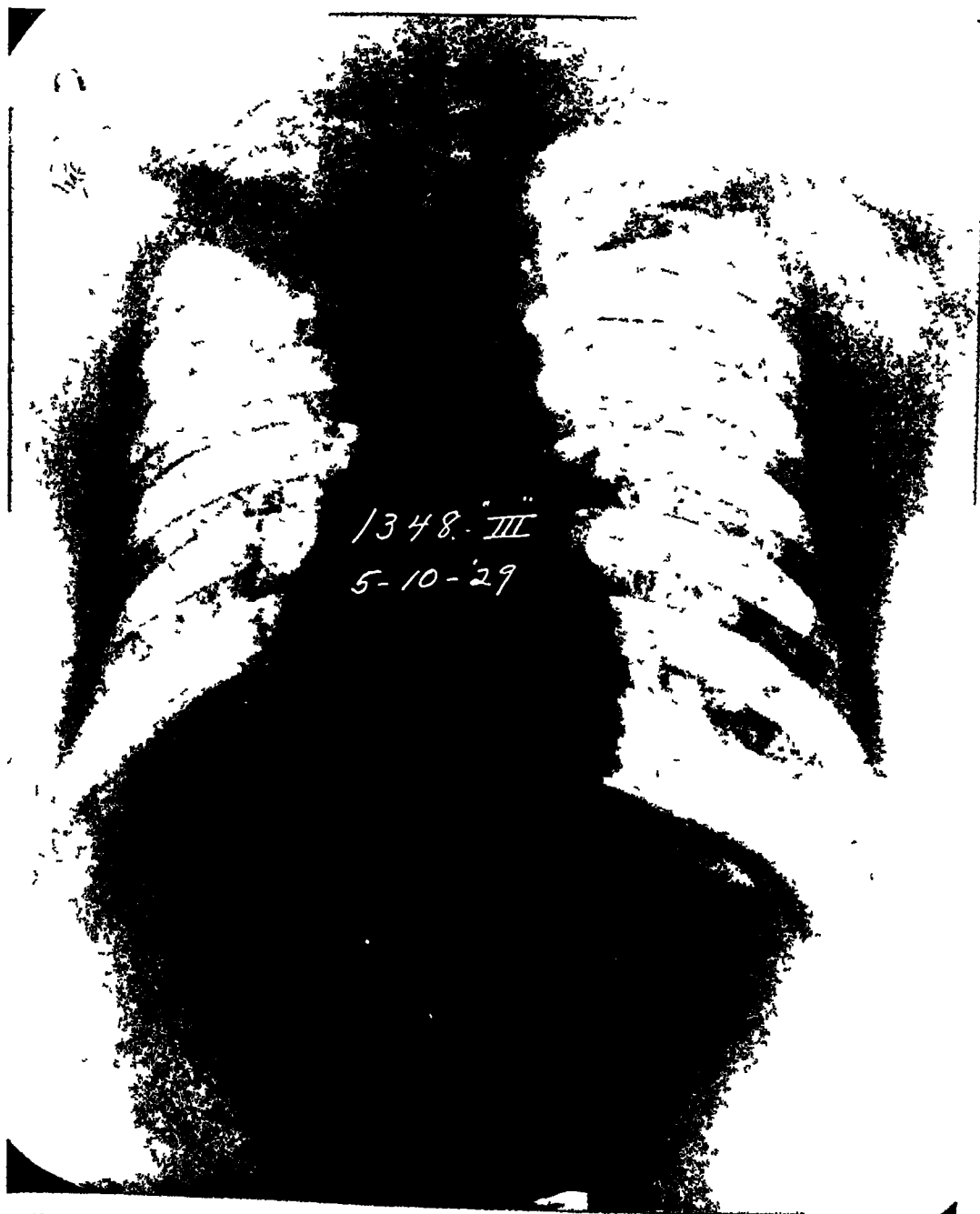


FIG 7 C, May 10 1929 shows the beginning of resolution in the middle portion of right lung, pleurisy over the apex

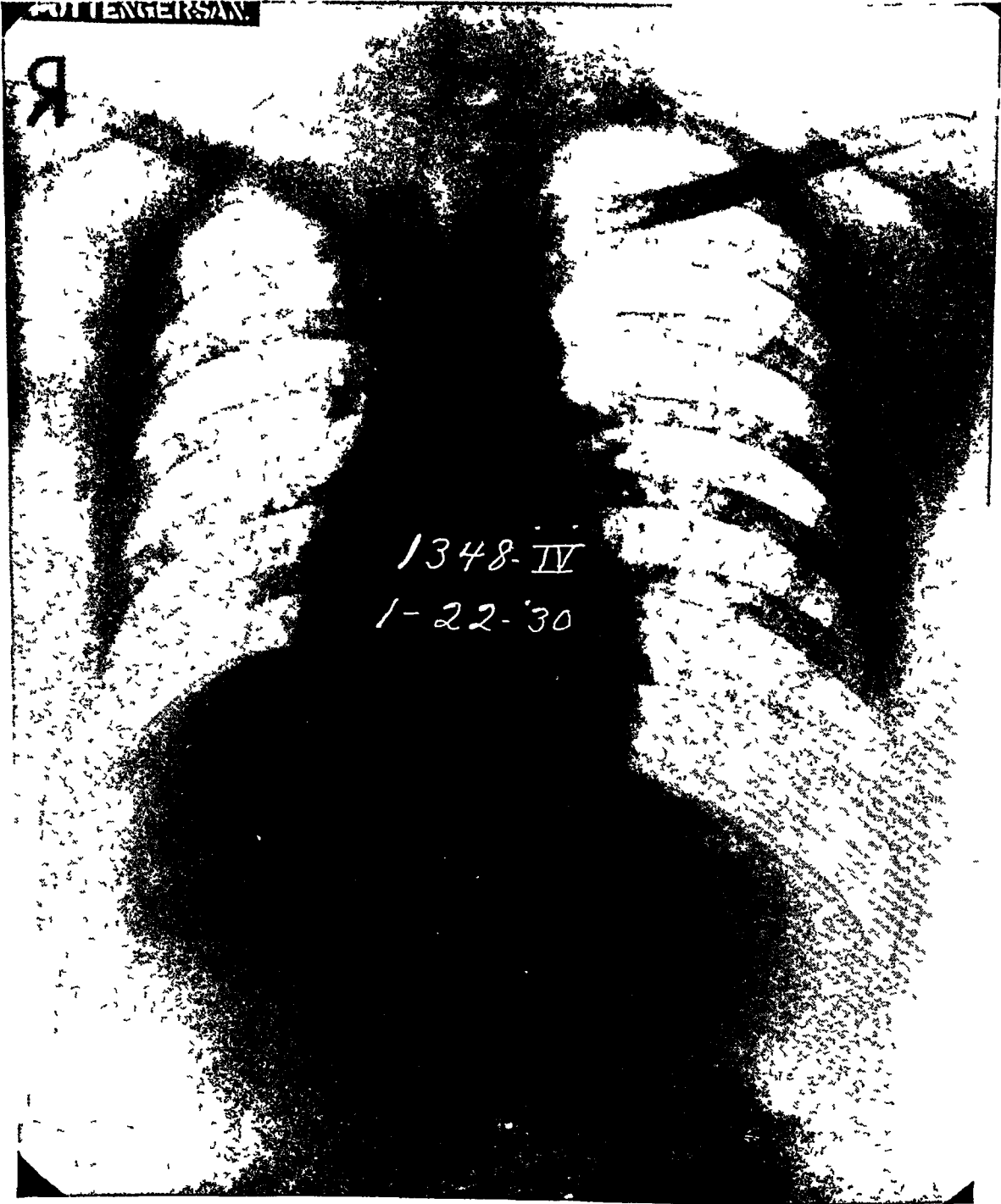


FIG 7 D, January 22, 1930, shows almost complete absorption of exudate through right lung

**POTTENGER SANATORIUM FOR DISEASES OF THE LUNGS AND THROAT**  
MONROVIA, CAL.

### TEMPERATURE CHART

DECEMBER-27-1928 to  
DATE-APRIL-29-1929- 192

NAME MR. S.H.

NO 9395

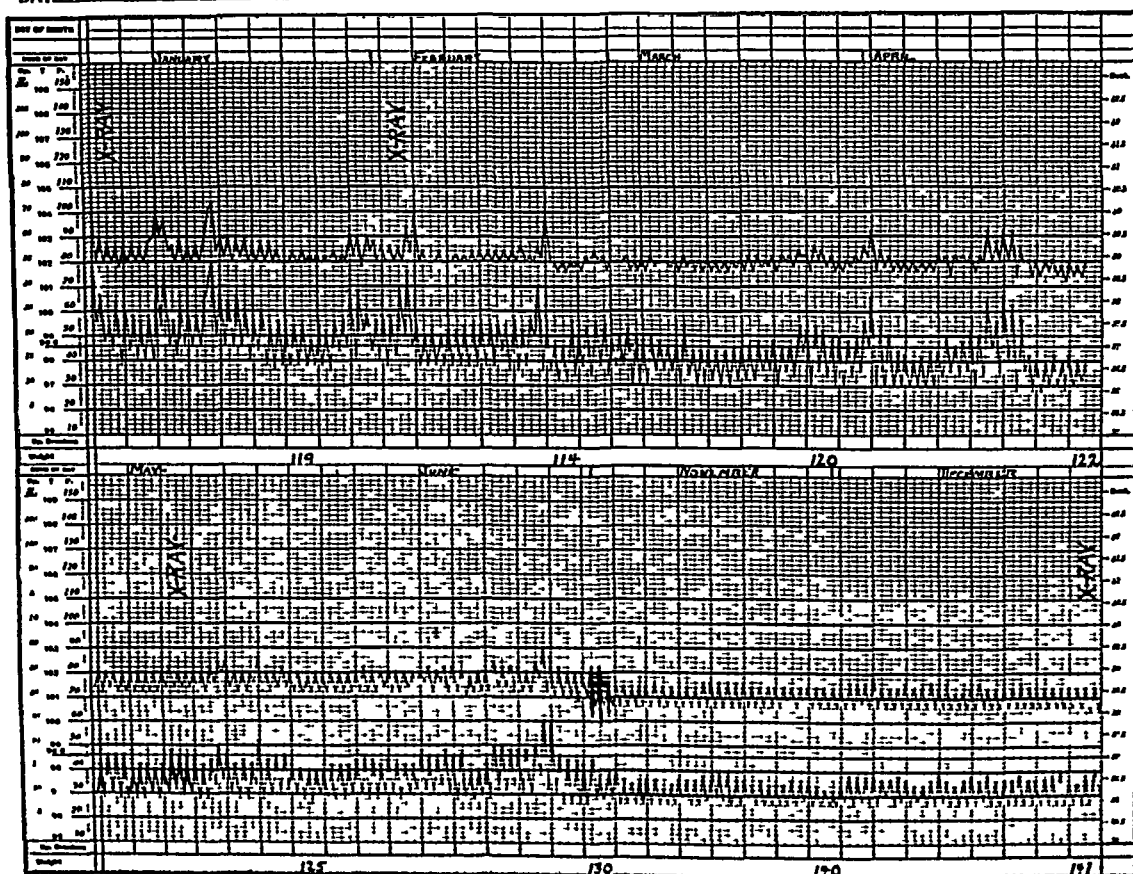
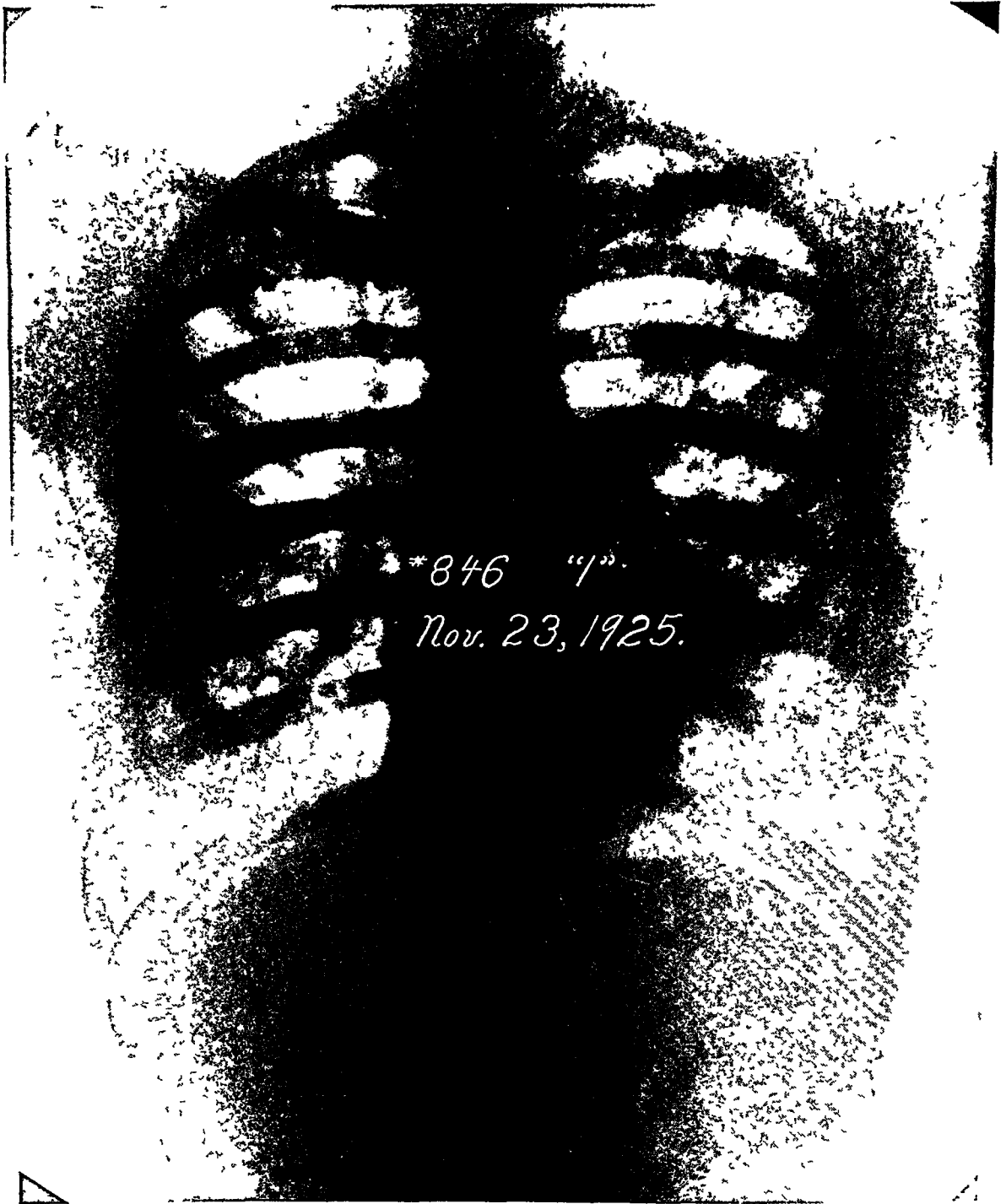


Fig 8 illustrates the temperature and pulse of the patient whose films are shown in Fig 7 A, B, C and D. Patient had constant temperature during first two months, followed by remission during the third month, and again followed by two periods of prolonged temperature in the latter half of the third and fourth months.

Temperature then dropped, remaining below normal for the most of the time except during early May and the latter part of June. Temperature again dropped to below normal, where it remained, as is shown in the latter portion of the chart.

Patient's weight decreased from 119 to 114 during the first two months. After that patient made steady gain in weight until 141 lbs was reached January 1920.

Sputum December 1928, 160 cc in 24 hours with 250 tubercle bacilli per microscopic field, December 1929 2 cc in 24 hours with 30 tubercle bacilli per microscopic field



FIGS 9 A and B illustrate an extensive fibrocaceous tuberculosis with marked allergic exudative inflammation, which healed under regular sanatorium regimen, without mechanical interference. Sputum became negative.

FIG 9 A, November 23, 1925, shows extensive exudative process in both lungs.

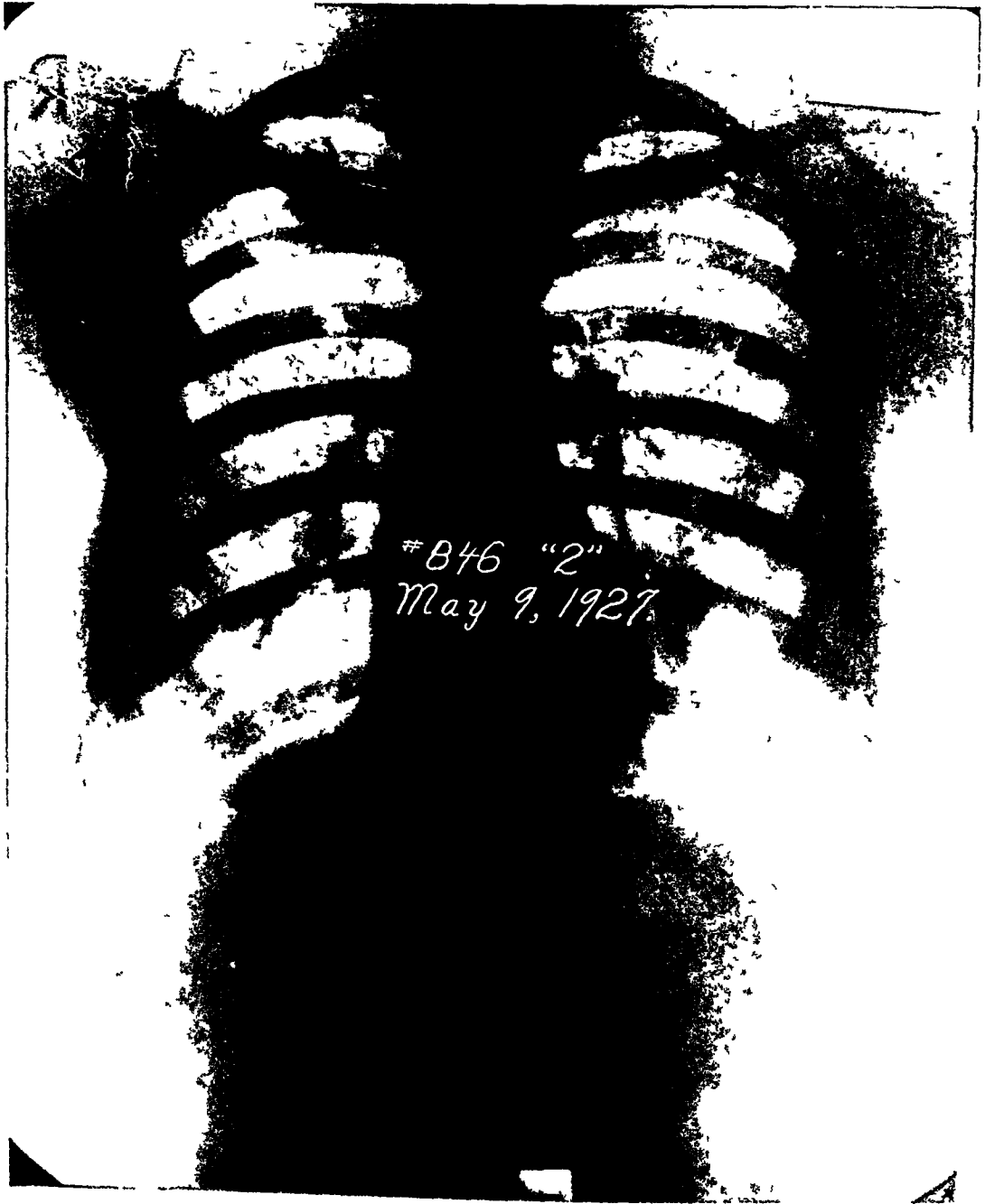


FIG. 9 B May 9, 1927, shows a very marked clearing, although marked shadow due to proliferative process and also deposits of calcium remain in the upper portion of both lungs. Marked pleuro-pericardial adhesions on left side will also be noted.



reinoculations accompanied by marked allergic response. Toxicity is marked, and even with moderately low temperature, they continue to show toxic symptoms. Healing under these circumstances usually fails. We must either assume that the lesion is caused by bacilli of unusual virulence, or that the numbers of bacilli in the reinoculations are extremely large, or that the resistance on the part of the individual is very low, or it may be that all of these conditions are present. The case which follows illustrates this type.

*Case No 9443 Miss M W Fig 10, A, B, C, and D, illustrates an acute onset with an exudative lesion in the upper portion of the right lung, which went on to cavitation and death of the patient in spite of treatment. This patient had been working up until two weeks before she entered the sanatorium. Film A was taken February 17, 1929, when patient was having considerable temperature. This went on to cavity formation, regardless of treatment, as shown in film B, taken May 20, 1929. Film C, taken August 27, 1929, shows an increase in the exudative reaction in the upper portion of the right lung, and film D, taken October 7, 1929, shows a very extensive excavation of the right apex. It will be noted, however, that in spite of the severity of the disease there was very little extension of infection in the left lung. Not until film D was taken was any particular extension shown, and this was taken only about three weeks before death, following a general breaking down of the patient's resistance.*

Preponderantly fibroid lesions are usually spoken of as being the most favorable type. This is probably due to the fact that they exist for a long period of time and are of a milder degree. The difficulty with a preponderantly fibroid type, however, is that the patient is apt to delay treatment until he is seriously handicapped by

extensive fibrosis, general emphysema, pleural adhesions, and until the disease is beginning to take upon itself more active and destructive aspects, all of which produce permanent and serious effects. The patient can live comfortably with this form of the disease for a long time, but from the standpoint of healing, it has been my experience that it is not so favorable, or at least not more favorable than the more acute types, because the latter will heal and leave a much freer lung field than the preponderantly fibroid type.

*Case No 9438 Mr A R Fig 11 A, B, and C, represents an extensive lesion preponderantly proliferative in character. This patient had been working continuously, free from symptoms of any character, until a hoarseness was noted, which interfered with his work as a salesman. On consulting a throat specialist, an ulceration was found in the larynx, which involved the cords and arytenoids, and on examination of the chest revealed an extensive lung involvement. The extent of this is shown in Fig 11, film A, taken February 12, 1929. It will be noticed that there is an exudation of mild degree in numerous areas on this plate, in both lungs, although the process as a whole is preponderantly proliferative. This patient improved satisfactorily under sanatorium regime, as may be inferred from film B, taken August 7, 1929, and film C, taken January 22, 1930.*

This case illustrates how the lung fails to clear in a preponderantly proliferative lesion, even though healing has been attained. New tissue has been formed, which replaces the elastic tissue of the normal lung. Although healing is nearly accomplished, as shown in film C, many shadows continue to show. Contrasting this with the preponderantly exudative types Figs 3, 4 and 9, it will be seen that in



FIGS. 10 A, B, C, and D show an acute exudative lesion involving upper half of right lung and middle portion of left lung, which extended regardless of treatment. Patient died from extension of disease with meningeal involvement. Patient was not able to muster sufficient resistance to bring the disease to a standstill.

Fig. 10 A February 17, 1929 shows acute exudative lesion in the upper half of right lung with cavity formation near apex, a moderate lesion in the middle of left lung. Patient was severely toxic.



FIG 10 B, May 20, 1929, shows increase in exudation and cavity more definitely formed, lesion in right lung much the same as in Fig 10 A

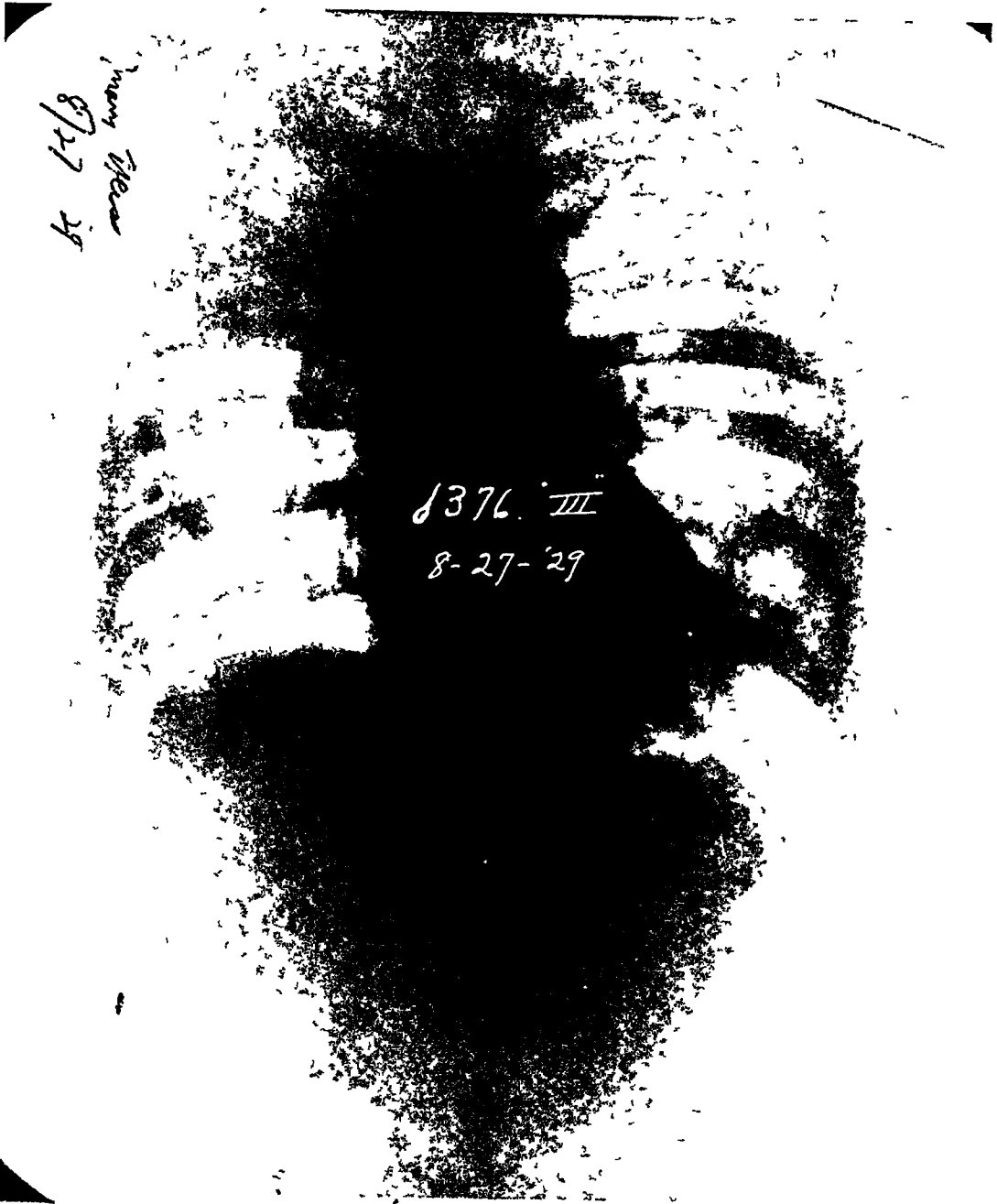
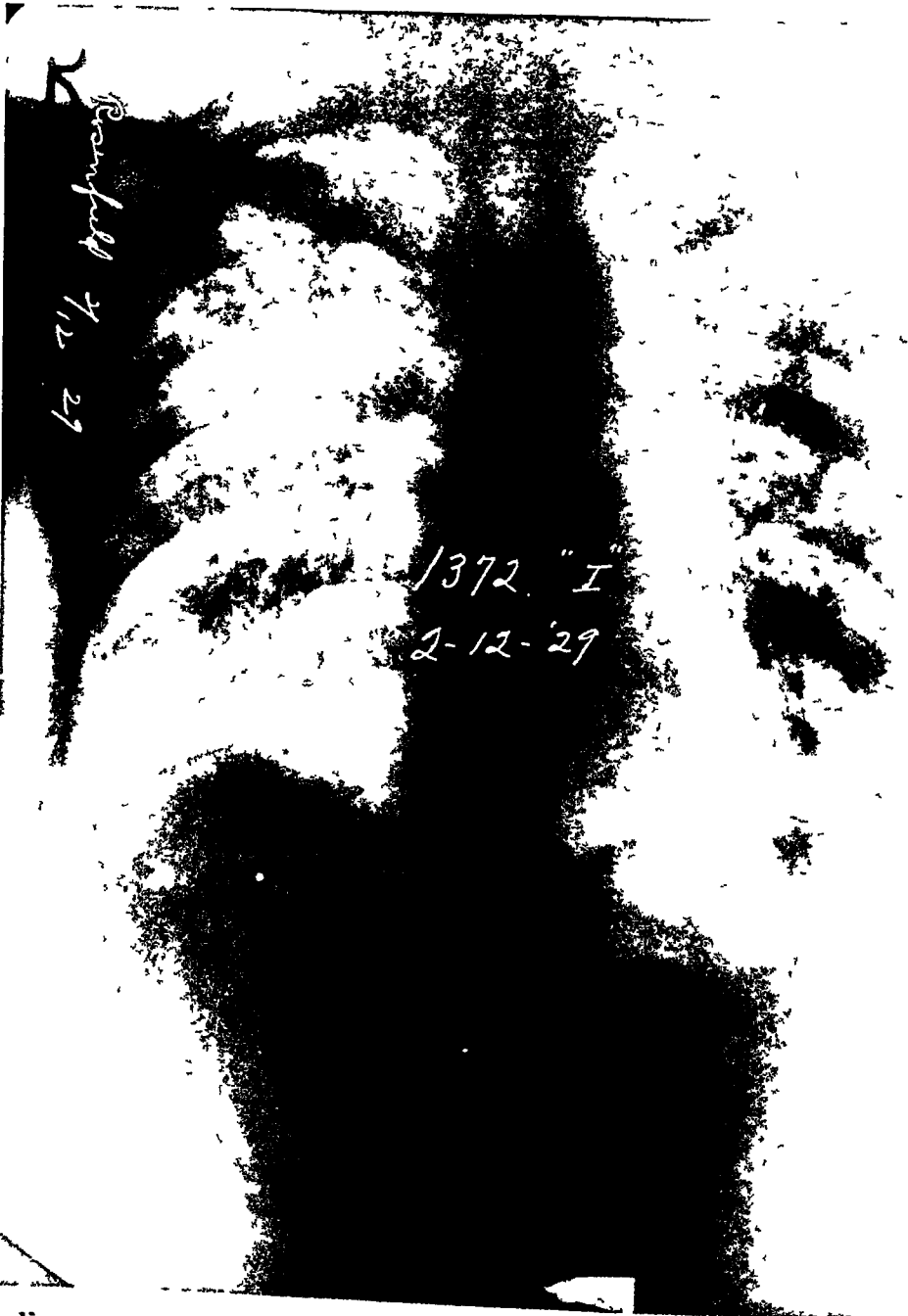


FIG 10 C, August 27, 1920, shows the lesion still markedly exudative, extension of infiltration in left lung

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FIG 10 D, October 7, 1929, shows a more definite excavation in upper portion of right lung, some disappearance of the pleural haze, very marked extension in left lung



FIGS. 11 A, B, and C represent preponderantly proliferative lesion. Regardless of the extent of the lesion as shown in Fig. 11 A, February 12, 1929, patient did not know he was ill until hoarseness from laryngeal ulceration developed one week previously. Excessive proliferation is shown through the major portion of both lungs with areas of increased condition scattered through.



FIG 11 B, August 7, 1929, shows resolution of a considerable portion of the exudation



FIG. 11 C, taken January 22, 1930, shows a continued resolution but the lung fields still show extensive shadows due to the chronic proliferative process. Such lesions have far more evidence of infection in the lung than do the preponderantly exudative type which clear largely by resolution.



the latter the lung field clears, leaving very few shadows on the plate.

We are probably justified in assuming that the difference between a preponderantly exudative and a preponderantly proliferative lesion is a difference in the specific defense. In the preponderantly exudative type we have a higher sensitization of cells and a more active allergic reaction. In the preponderantly proliferative type sensitization is much less in evidence and the allergic reaction only takes place to a minimal degree. The difference in the lesions might be due to a difference in the virulence of bacilli, a difference in reaction on the part of the patient, or to the establishment of a more complete immunity, in which sensitization and the allergic inflammatory process take a lesser part. In the preponderantly proliferative group, the toxic symptoms are usually mild, in fact, they are often absent until the disease becomes very extensive, while in the exudative group, the toxic symptoms are marked and come on early.

From these illustrative cases it may readily be seen how tuberculosis tends to heal under favorable conditions, how the patient may become desensitized to his own and to bacillary protein, which enables him to withstand severe disease for long periods of time, and too, how, now and then the disease will spread and cause a severe

and fatal illness without calling out an effective specific resistance.

### SUMMARY

1. Tuberculosis heals as a result of the patient's immunity reaction
2. The efficiency of the immunity reaction is increased by repeated reinoculations
3. The effects of immunity are shown in the following services rendered to the host
  - (a) Destruction of bacilli
  - (b) Retardation of the passage of bacilli through the tissues
  - (c) Elimination of bacilli through natural channels by caseation and cavity formation
  - (d) Development of a state of desensitization to bacillary and non-bacillary toxins
  - (e) Encapsulation or rendering inactive viable bacilli which remain in the tissues
  - (f) Ridding the body of the inflammatory products which accompany the infection
  - (g) Repair of the injury inflicted upon the body by the disease
4. Treatment is efficacious to the extent that it is able to limit reinoculations of bacilli and bacillary protein to a minimum and create within the patient a resistance capable of coping with them as they occur

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## Editorials

### *RECENT STATISTICAL STUDIES OF CANCER PROBLEMS*

Greenwood has reviewed the papers and monographs published within recent years utilizing mainly or wholly a statistical method, which, in his opinion, have advanced our knowledge of some aspect of the problem of malignant disease. As he himself admits the selection of the articles reviewed may be colored by his individual predilection, but it is possible that such a review, however incomplete and even biased, may be interesting and of some service to the general reader. The first topic considered in his review is the alleged increase of cancer. By all lay writers, and a majority of medical writers the recorded increase in the cancer mortality rate has been accepted, if not precisely at its face value, at least as reflecting a substantial change of incidence with time. From this point of view a minority of competent statisticians dissent and endorse the view of King and Newsholme that the recorded increase merely reflects improvement in the certification of causes of death. They argue that the significant increase of cancer mortality is borne by the sites less accessible to examination, and therefore

such that diagnosis would become less difficult with the improvement of medical technique and diagnosis. On the other hand, Stevenson has pointed out that neither in English or American experience is it true that the rate of increase in cancer of inaccessible sites has uniformly been greater than that of accessible sites. Schereschewsky and Dublin concluded that when reasonable allowance was made for errors and changes in sex and age constitution of the population a real increase of rate of mortality with time persisted. The balance of opinion inclines towards the conclusion that the rate of mortality from cancer as a whole has really increased. At the same time it is recognized by those who hold that opinion, that in most all countries the recorded changes during the last generation, perhaps, over-state the real change. It is further to be remembered that the increase has affected the older age groups and is coincident with a fall in the mortality rate from all causes together. A larger proportion of persons now live to the "cancer age" who formerly died in earlier life, and the quality of these survivors may be different from that of persons in the decline of life 50 years ago. Greenwood sums up the matter by the statement that it appears that there has been no decrease and probably an increase of the real rate of mortality from cancer, but the records of the

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\*A Review of Recent Statistical Studies of Cancer Problems. By Major Greenwood (Studies on the Diagnosis and Nature of Cancer. Wm Wood & Co, 1930, p 95)

most highly developed systems of vital statistics show that this increase is slowing down. In all countries down to very recent times, the rate of mortality from cancer was returned as being higher among women than men, but this is no longer universally true. There is little doubt that the factor of improved diagnosis, to which the whole increase of cancer mortality has been attributed by some, is partly responsible, since cancers of the breast and uterus which form so important a part of the gross mortality from cancer in women, are relatively easy to diagnose, so that a smaller proportion of missed cases occurred in the past in cancers of females than of males. Modern statistics confirm also the earlier conclusions as to the greater liability of married women to cancers of the uterus than of unmarried. As to the effect of occupation and social status upon cancer mortality, the most recently analyzed figures show a regular increase from the highest to the lower social grading. The class most prosperous shows the lowest cancer mortality. It has further been found that when this social distribution was analyzed as to the different sites of cancer, differentiation proved to be confined to certain sites accounting in all for about half of the total mortality. These sites include the alimentary tract from mouth to stomach, the skin and the larynx. Sufficient data have not yet been collected to prove the susceptibility or immunity to cancer in different races. This question is still open. A similar uncertainty attends the statistics of cancer mortality as affected by locality. No very definite

conclusions have emerged from statistical studies carried out along this line. The same may be said as to the contrasting rates of mortality in villages, streets and houses. The meaning of the apparent bias of the distribution cannot as yet be ascertained. We do not know yet whether certain houses have an apparently undue proportion of deaths from cancer, because there is some peculiarity in the houses themselves, or whether these chanced to be houses occupied by an abnormal proportion of persons living at the cancer age. As to the old idea that a meat diet predisposes to cancer, an enquiry into the cancer mortality among the members of various vegetarian orders showed that cancer undoubtedly occurred in the members of such and that there was no indication that the position of cancer relatively to that of other causes of death was in any way exceptional. This enquiry did not, therefore, confirm the belief that a meat diet predisposes to cancer. Great divergences exist between the rates of mortality from cancer of the female breast and uterus in the three countries, England and Wales, the Netherlands, and Italy. The reason for this divergence has been the object of a prolonged international enquiry carried out under the auspices of the Health Section of the League of Nations by representatives of the three countries. This investigation has thrown much light on related topics but has failed to explain the fundamental differences. Here too it does not seem that the problem can be solved by means of purely statistical investigation. A good deal of recent

work has been done on the relative frequency of cancer in native races. The general result has been that all forms of malignant disease seen in civilized countries occur in native races, but that the proportional frequencies of different varieties are different. A careful enquiry by Hoffman respecting the incidence of cancer in the American Indian, suggests that the incidence of cancer is low, but fails to establish any definite association between either the consumption of meat or the prevalence of constipation and the cancer mortalities of different tribes. It is Greenwood's opinion that the data at present available are altogether insufficient to form the basis of any induction. The surgical statistics of cancer have attempted to answer such questions as: What is the average length of life of persons suffering from different forms of malignant disease who are not treated by any method designed to remove the disease? What is the advantage of surgical treatment adopted at different stages of the disease? Comparative advantages of the knife and radiological treatment in different forms and at different stages of cancer? Proportion of cancer cases receiving early treatment, and how may that proportion be increased? From various papers on cancer of the breast and uterus the conclusion may be reached that early radical operation in cancer of the breast means an average prolongation of life of more than ten years, and it is probable that in cancer of the uterus the results are little less favorable. There is evidence of a clinical statistical character that radiological treatment can compete fa-

vorably with treatment by the knife of cancer of the cervix uteri. It has been shown that the proportion of patients who present themselves for treatment only when the disease has advanced beyond the reach of surgical art is very large. How this proportion can be reduced is the great problem. It is obvious that none of the statistical investigations so far carried out, taken by itself, has changed our scale of values, but the cumulative effect of these laborious studies, on the positive side, has increased the precision of our knowledge of the incidence and distribution of cancer, while on the negative side, it has shown the false foundations of many popular theories and superstitions regarding cancer. It is probable that through the gradual improvement in accuracy and completeness of the medical statistics of all nations the way can be best prepared for a really illuminating survey of the cancer problem. At the present time little more can be hoped from the statistical method than an impartial study of strictly defined problems. The time is still far distant when the data of all civilized countries and of all subdivisions of these countries will be strictly comparable in value and significance.

#### *FURTHER REPORT ON VACCINATION WITH B C G*

In an editorial in the August number of the *Annals* we gave an account of the Lubeck disaster in the vaccination of 246 children in that city with the bacillus-Calmette-Guerin, with the result that up to March 25 there had been 17 deaths from alimentary tuber-

culosis, with 41 living showing evidence of tuberculosis. Later reports show that up to June 3th, 46 children were reported as having died with acute tuberculosis of the alimentary type, and 68 were seriously ill at this time. Much excitement was naturally created by this unfortunate tragic outcome of vaccination against tuberculosis. The affair has received much attention in the press throughout Europe, and has been debated in the Lubeck Parliament. It is reported that criminal proceedings for bodily injury have been started against the medical director of the Lubeck Health Office and the chief physicians of the State and Children's Hospitals. From the Pasteur Institute come strong statements by Calmette as to the harmlessness of his vaccine, and the assertion that the Lubeck accident could only have occurred through an error in the preparation of the vaccine in Germany. Contamination of the BCG culture sent from Paris with virulent human tubercle bacillus in the laboratory in Lubeck has been more than hinted at. Unfortunately following the Lubeck occurrence much publicity has been given in the European press to a situation that has arisen in Ujpest, a town near Budapest. Several hundred children had been vaccinated with the BCG vaccine and of these six have died with clinical tuberculosis, although this is not convincing proof that these deaths can be attributed to the vaccine, yet because of the Lübeck disaster vaccination with BCG has been stopped in this town. If these deaths can be shown to have been a result of the vaccine, the case against the use of the

BCG vaccine becomes very serious indeed. Further, wholesale vaccinations with the Calmette-Guerin organism should never have been undertaken as long as there was any doubt anywhere that the BCG strain is a fixed one, and cannot be converted into the human form. Laboratory workers are divided on this extremely important point. Petroff, of Saranac, reported that he had cultivated virulent bacilli from Calmette's BCG vaccine by his isolation of two kinds of colonies "R" and "S", the latter being virulent, and his work has been confirmed in Canada by Read. Watson of the Federal Research Laboratories at Hull has shown that BCG is virulent for calves, and he is convinced that BCG is not a fixed virus. On the other hand, Lange, in a report to the German Health Office maintains that BCG organism is never converted into the human type. He criticizes Petroff's work as wrong, having been based on the study of cultures contaminated with human bacilli as stated in our previous editorial. Lange regards the Lubeck tragedy as due to the use of a vaccine contaminated with a virulent human strain. How the contamination occurred he is either unable or unwilling to say, but the inference is that the contamination occurred in the laboratory in Lübeck. Surely a Commission should be appointed to settle the question as to the fixed avirulent nature of the BCG vaccine. The question is too important to go begging, or to be allowed to remain in a position of the slightest doubt. If the Calmette claims for the favorable result in thousands of vaccinations already made, without ever a bad re-

sult, can be proved beyond any doubt to be true, then the BCG vaccine is surely a tremendous advance in the fight against tuberculosis; and its value should not be clouded by any suspicion or distrust. On the other hand if the BCG organisms can under any conditions be convertible into virulent tu-

bercle bacilli, human vaccination with them should cease, as being only of the nature of human experimentation, too serious in its possibilities of outcome to be permitted. It is strongly to be hoped that active steps may soon be taken to clear up this ambiguous situation

## Abstracts

*Studies on the Circulation of the Feet in Diabetes Mellitus with and without Gangrene* By ISAAC STARR, JR., (Amer-Jour of the Med Sc., August, 1930, p 149)

In a series of 100 unselected diabetics under treatment the response to the skin of the lower extremities to histamin under standard conditions indicated that 32 percent had a normal circulation in their feet, in 34 percent the circulation was somewhat impaired, in 34 percent markedly impaired. The caloric output of the feet was determined 30 times in 8 diabetics, it was constantly below normal in 6 patients. It is concluded that the majority of diabetics have an abnormal low blood-flow through their feet. The circulation in the feet of certain diabetics may vary markedly with their general condition, but in certain arteriosclerotic diabetics improvement in general condition is not followed by improvement in circulation to the feet. The reaction of the skin of the feet to histamin together with the physical findings permits the demonstration of the presence or absence of adaptations to compensate for sclerotic narrowing of the large arteries, and allows the clinical detection of pathologic change in the minute vessels when the larger arteries are not notably involved. In certain cases the presence or absence of local vasomotor reflex responses can be demonstrated. Such demonstrations permit the assignment of individual cases to one of a number of groups. The great majority of patients with trouble with their feet or history of it fall into two groups characterized by markedly abnormal histamin reactions and generalized arteriosclerotic changes. The data plainly imply that by considering the histamin reaction together with the physical findings a more accurate prognosis can be made than by considering either separately. The types of histamin

reaction occurring on the legs of 14 patients with gangrene of the feet are described. The value of this evidence in the selection of treatment and the choice of level of amputation is discussed. An abnormal histamin reaction appears to the author to contraindicate amputation at that level, but a normal reaction is not a guarantee of success. Other factors, the age and strength of the patient, the duration of the disease, the condition of the heart, vessels and blood pressure should be taken into consideration as well as local vascular conditions. The conclusions in this paper are based on reasoning rather than on the data, data on the prognostic significance of the histamin reaction will accumulate but slowly. In the meanwhile it has been found that the response of the skin to histamin together with the physical findings permits an analysis of the conditions of the circulation in the extremities which cannot be obtained by physical examination alone.

*The Age and Sex Distribution and Incidence of Neoplastic Diseases at the Memorial Hospital, New York City* By GEORGE G. PACK and ROBERT G. LEFEVRE (Journal of Cancer Research, June, 1930, p 167)

During a 12 year period, 19,129 tumors were studied at the Memorial Hospital, 16,565 were malignant. Malignant epithelial tumors composed 89.6 percent of this number, 10.4 percent were sarcomatous. The average age of all the patients was 53.9 years. The average age of the patients with sarcomas was 38.2 years. During the last 75 years there has been no appreciable change in the average ages of occurrence of the more common neoplasms. The decennium 40-50 marks the period when cancer frequency makes its first tremendous increase. Cancers develop in such organs as the breast, thyroid, stomach and prostate,



which undergo physiologic atrophy at definite periods in the life history of the individual have specific relationships to age. The majority of the remaining malignant epithelial tumors are not related to age except that the passing years afford sufficient time for the causative factors to induce degenerations, tissue over-growth, and even cancer. There was evidence to prove that chronologic age is not so important as anatomic and physiologic age as an etiological factor in cancer. The five most common malignant tumors in infants and children were Wilms' adenomyosarcomata of the kidney, ocular glioma, teratoma testis, endothelial myeloma and thymoma. The age incidence of certain cancers increases each year until the normal span of human life is reached. These cancers were melanomas, basal-cell epitheliomas, squamous cell carcinomas of the lip, penis, floor of mouth, buccal mucosa, and inferior alveolus. When percentage corrections are made for the incidence of the various sarcomas on the basis of the proportionate number of persons living during the age periods, it is seen that the incidence of these malignant connective tissue tumors varies only slightly from age 20 to age 80. The benign papillomas of many organs always occur at younger average ages than the carcinomas of the same organ, e.g., the age variance of 22 years for the larynx, 17 years for the vulva, 7 years for the urinary bladder. The tumors which occurred predominantly in females were: mammary adenofibroma, carcinomas of the breast, thyroid, urethra, appendix, and gall bladder. The tumors which occurred predominantly in males were chondroma, laryngeal papilloma, papilloma of urinary bladder, thymoma, lymphosarcoma, neurogenic sarcoma, bone sarcoma, multiple myeloma, hypernephroma, squamous celled carcinoma of skin, basal-cell epithelioma, carcinomas of the lip, larynx, tonsils, tongue, buccal mucosa, esophagus, stomach, rectum, liver, pancreas, and urinary bladder. There was a constant age difference of  $2\frac{1}{2}$  to 4 years for the average ages of male and female patients with the same regional and histological types of cancers, the females were younger than the males. The liability

to epidermoid carcinoma of the skin was greatest after the age of a century was passed. Thirty percent of all malignant tumors in patients over 74 years were basal-cell epitheliomas. Brain tumors were uncommon in old people, none occurred in patients over 70 years. Fifty percent of the gliomas were in subjects younger than 25 years. Chondrosarcoma was the only malignant connective tissue tumor which did not appear in children, the youngest patient was aged 22 years. Giant-cell tumors were the only bone tumors which occurred with greater frequency in females. Contrary to general opinion, bone sarcomas were relatively as frequent at ages 60-64 as at ages 15-19 years. The average age of persons with Ewing's endothelial myeloma was 22 years, the average age of persons with multiple myeloma was 42 years. Carcinoma of the alimentary tract was four times as frequent in men as in women. As far as the ratio of sex was considered, the major liability of the male to cancer of the alimentary tract seemed gradually to approach the female liability from the mouth downward through the digestive tube. Forty-eight percent of the cancers in males were in the alimentary tract and accessory organs. The adenoid cystic epithelioma of mucous membranes is explained by the Durante-Cohnheim embryonic theory of tumor origin. In subjects younger than 25 years carcinoma of the tonsil was 13 times as frequent as carcinoma of the tongue. At the age of 75, carcinoma of the larynx was 32 times as frequent as at age 25. For papillomas of the larynx, the male preponderance was 2 to 1, for carcinomas of the larynx, the male preponderance was 10 to 1. There was evidence to prove the existence of a definite group of carcinomas of the nasal mucosa in children. The average age of patients with carcinomas of the parotid gland was 10 years older than for patients with mixed tumors of the parotid. Carcinoma of the esophagus was very rare in young people, and was quite infrequent in elderly people. Of all cancers of the gastro-intestinal tract, carcinoma of the appendix occurred at the earliest average age, namely 32 years. One out of every 25

patients admitted to the hospital had carcinoma of the rectum. Epidermoid carcinoma of the anus occurred at the youngest average age, of all the regional locations of this histologic type of cancer. Among 100 regional and histologic varieties of cancer, carcinoma of the prostate occurred in patients of the oldest average age, namely 63 years. Yet the incidence for this carcinoma did not increase with advanced age. Teratoma testis is essentially a disease of young men, the incidence declined rapidly after the age of 35. Of all tumors of the female genitalia, vulvar carcinoma occurred in subjects of the oldest average age, namely 60 years. The percentage of vulvar carcinomas occurring in single women was high (16.2 percent). Carcinoma of the cervix uteri was twice as frequent after age 75 as before age 25. The percentage of carcinomas of the body of the uterus in single women was 4 times as great as the percentage of carcinomas of the cervix in single women. The ovary was the only organ in the body wherein the benign and malignant epithelial tumors affected subjects of the same approximate age. The incidence of mammary adenofibromas gradually increased from age 20 to age 50. These fibroadenomas occurred in subjects who averaged 15 years younger than the patients with carcinoma of the breast. One out of every 7 patients admitted to the hospital had mammary cancer. Thyroid adenomas in males have a greater tendency to become carcinomatous than the thyroid adenomas in females. Tumors of the sexual organs occurred at younger average ages in single than in married people, e.g., mammary fibroadenoma and intraductal papilloma, sarcoma of the breast, teratoma testis, carcinomas of the penis, prostate, vagina, cervix, ovary and body of uterus. Cancers of early life, as in breast, stomach, tongue, and rectum, progress more rapidly, disseminate more frequently and recur more often after removal than do their congeners of adult life. Radio-sensitivity is a property found frequently in the malignant neoplasms of youth. Fever is significantly frequent in the case of rapidly growing malignant tumors in young people.

*Malaria Treatment of Paresis* By WALTER FREEMAN (The American Journal of Syphilis, July, 1930, p 326)

Freeman concludes from his study that malaria frequently brings about a suppression of the inflammatory manifestations of paresis, and in the successfully treated cases when death results it is often not from causes connected with the nervous system. Nevertheless, examination of the other organs of the body indicates that the syphilitic infection is still present, and it may show marked activity, particularly in the circulatory system and in the liver. In the small series of cases available for complete study there are indications that syphilitic lesions outside the nervous system are more frequent and sometimes more severe in cases where the malaria had brought about a satisfactory remission in the cerebral inflammation, but this finding may rest upon the relatively greater age of the subjects examined. Extranuclear disease in certain of these cases presumably antedated the therapeutic attempt. The malaria is not to be blamed for the occurrence of certain of the late complications such as cirrhosis of the liver. Patients with aortic or myocardial disease often come through the malarial rigors surprisingly satisfactorily, but if the liver is damaged, the outlook is less favorable. Patients subject to convulsive seizures are bad risks, not so much from the malaria itself as from the frequent attending complications. Possibly if due attention is paid to the suppression of these convulsive seizures by control of fluid intake, the results might be better. There are several ways in which the malaria may operate: first, by killing the spirochetes by the high temperature record, second, by stimulation of the reticulo-endothelial system, and third, by the forced drainage of the nervous parenchyma along the perivascular channels into the subarachnoid space. The theory is advanced that the pruritus of fibroblastic tissue in the neural parenchyma may prevent the spirochetes from lodging in the brain nests protected from the activities of the fluids and wandering cells, whereas the infection may persist in other organs due to the presence of this tissue. In an untreated percentage of cases there were

to be sterilization of the syphilitic infection throughout the body as induced by the return of the serologic reactions to negative. The influence of previous treatment and especially of arsenical treatment cannot yet be evaluated. The figures of certain authors comparing the results of malaria in cases that have received no previous treatment as against those that have received arsenical treatment, cannot be taken at face value unless the time element is properly evaluated, but the figures are suggestive of the possibility of arsenicals preventing the full beneficial action of the malaria. The most outstanding failure of the malaria series was one that had had the most intravenous treatment, and some of the most successful cases had received no treatment before malaria. Antisyphilitic treatment following the exhibition of malaria would seem to be indicated on account of the occurrence of significant lesions outside of the nervous system. The suggestion is made that such treatment should be delayed until some time has elapsed in order to determine by serologic tests whether the activity of the syphilis, serologically speaking, is subsiding sufficiently rapidly. Other pyretogenic agents besides malaria are un-

doubtedly effective in the treatment of paresis, but there are indications that malaria combines most favorably the three factors suggested above as the means of suppressing the activity of the spirochetes in the central nervous system.

*The Value of Histamine as a Test of Gastric Secretion From a Physiologic Point of View.* By B. P. BABKIN (The Canad Med Assoc Jour, Aug, 1930, p 268)

Babkin's summary is to the effect that the subcutaneous injection of histamine stimulates the secretion of gastric juice. The acidity of this juice is normal, but its digestive power and content of organic substances is lower than in juice obtained by sham-feeding. The supposition is that histamine activates chiefly the parietal cells of the gastric glands, producing the solution of hydrochloric acid, and in a much lesser degree the peptic and mucoid cells, which supply the juice with enzymes and organic substances. The histamine gastric secretion, therefore, represents largely one particular function of the gastric glands, and does not give a true picture of the total activity of the glands.

## Reviews

*Tropical Medicine* By SIR LEONARD ROGERS, C.I.E., M.D., B.S. (Lond.) F.R.C.P., F.R.C.S., F.R.S., Major-General Indian Medical Service, Ret. Medical Adviser to the India Office, Physician and Lecturer, London School of Tropical Medicine, Lecturer on Tropical Medicine, London School of Medicine for Women, Late Professor Pathology, Medical College, Calcutta, and JOHN W. D. MCGAW, C.I.E., V.H.S., B.A., M.B., B.Ch., B.A.O., Major-General Indian Medical Service Formerly Director and Professor of Tropical Medicine, Calcutta School of Tropical Medicine and Hygiene 536 pages, 77 illustrations P. Blakiston's Son and Co., Inc., Philadelphia, Penn. Price in cloth \$4.00 net

The writers of this book have had the advantage of many years' experience in clinical, pathological and teaching work in the Tropics. They are convinced that there is a real need for a small work on tropical medicine which will contain only such details of microscopical technique as the general practitioner can carry out in his hospital or practice, and will be devoted chiefly to the recognition and management of the diseases which are commonly met with in tropical and subtropical countries. Most of the works on tropical medicine extant assume that the facilities of up-to-date laboratories are at the disposal of medicine men in the tropics, whereas the truth is that at least 90 percent of the medical men in the tropics have to depend on their own resources and on the simple methods of diagnosis, which are within the reach of the general practitioner. The authors also feel that there is a need for a small and handy book which will give a broad survey of the field and so serve as an introduction to the subject of tropical medicine. Since in the great majority of medical schools and colleges there are special courses in pathology,

bacteriology, and entomology, much of the material covered by such courses is omitted from this book, as it can be found in the text books on these subjects. This book makes no attempt at completeness, many of the rarer diseases have not been touched on at all, and others have been dismissed in a few lines, and some diseases of considerable importance outside of the limits of the British Empire have received very brief notice. This book is written largely with reference to India, and especial attention has been paid to the geographical distribution of the more important diseases and to maps showing their distribution in that country. The diseases dealt with in this book are classified as far as practicable according to their causal agencies, but in some cases a clinical classification is followed as being more helpful to the student. The authors have retained the more generally known names of common tropical parasites rather than adopt the latest scientific nomenclature, such as "Wuchereria" for the more familiar *Filaria*. The treatment of the material comprises eleven sections: Febrile Diseases Caused by Protozoa; Febrile Diseases Caused by Spirochetes; Febrile Diseases of Uncertain Origin, The Typhus Fever Group, Bacterial Febrile Diseases; Bowel Diseases with Symptoms of Dysentery and Diarrhea; Diseases with the Most Prominent Lesions on the Surface of the Body, Helminthic Diseases, Diseases Caused by Venomous Animals, Diseases Associated with Diet and Diseases Caused by Heat and Light. This book is especially valuable as reflecting the experience of the authors in India, it is, of course, written largely from that standpoint, but the general material contained in the volume is of the greatest value to all physicians in tropical and subtropical countries. Especially valuable are the sections on the febrile diseases. No book on tropical medicine has

yet appeared which has such a foundation of practical experience beneath it. The reviewer regrets that the authors did not devote more attention to the pathology of the diseases peculiar to the tropics as that would have added greatly to the value of the work; but they have accomplished excellently what they set out to do in their emphasis of the clinical and practical aspects of tropical diseases. The section on Undulant Fever has not been brought up to date, in the light of American experience, but this again is excusable viewed from the standpoint of their idea of what they wished their book to present.

*Studies on the Diagnosis and Nature of Cancer* By Various Authors Being Reprints of Special Articles from the Cancer Review 240 pages, 22 illustrations William Wood and Co, New York, 1930 Price in cloth \$4.00

This book consists of reprints of articles, particularly on diagnosis, submitted for the consideration of medical practitioners and students of cancer problem. The British Empire Cancer Campaign is responsible for its publication. It contains the following articles. The Early Diagnosis and Treatment of Cancer of the Bladder by A Clifford Mason, The Present Position of the Operative Treatment of Breast Cancer by W. Sampson Handley, The Early Diagnosis of Cancer of the Colon by J P Lockhart-Mummery, Primary Carcinoma of the Lung with Special Reference to X-ray Diagnosis by P J. Kerley, The Early Diagnosis of Cancer of the Pharynx and Larynx by St Clair Thompson, The Metabolism of Tumors by R. K. Cannan; Heredity in Relation to Cancer by E. A. Cockayne, A Review of Recent Statistical Studies of Cancer Problems by M. Greenwood, Malignant Disease of the Thyroid Gland and Its Relations to Goitre in Man and Animals by C. Wegelin; The Metabolism of the Trophoblast by W. Cramer; Bone Sarcoma by A. Kolodny, and Immunity to Transplantable Tumors by W. H. Woglom. These papers are very unequal in interest and value. Mason's article on the early diagnosis and treatment of cancer of the bladder is short, concise, and to the point.

Handley's article on the operative treatment for breast cancer is also concise and presents the advantages of the diathermic knife as against cold steel. Cancer of the colon is well summed up by Lockhart-Mummery, but nothing new is offered. The article on primary carcinoma of the lung is a practical one and covers the ground very thoroughly. Not so much can be said for Wygard's article on the early diagnosis of cancer of the stomach. Of greater practical value is Thompson's article on the early diagnosis of cancer of the throat. Cockayne's article on heredity in relation to cancer presents a fair, though not over-enthusiastic, statement of the case. Of the remaining articles the one by Woglom on immunity to transplantable tumors is the most important, covering as it does the literature of the subject very completely. He concludes that immunity to transplantable tumors is a generalized refractory condition which appears to be entirely unrelated to other forms of immunity. No single organ has yet been proved responsible for its elaboration; nor is it affected by physiological conditions such as age or pregnancy. In its acquired form it is neither hereditary nor passively transferable through the body fluids. It seems probable that natural resistance is only the ability to react so promptly and efficiently that a graft is overcome before it gains a foothold. The outcome of inoculation is determined by an interplay between the hostility of the host and the proliferative vigor of the *implant*, hence an absolute immunity does not exist. Resistance is effective during the first few days following inoculation but entirely powerless against an established tumor. Nothing may accordingly be hoped for at present in respect to successful therapy from this direction. This volume is of interest to all concerned with the problem of cancer, either from the clinical side, or the pathological, or the experimental.

*The Mycoses of the Spleen* By ALEXANDER GEORGE GIBSON, M.D., F.R.C.P., Physician to the Radcliffe Infirmary and Reader in Morbid Anatomy in the University of Oxford 169 pages, 15 figures

The Macmillan Company, New York, 1930 Price in cloth, \$4.50

This volume is published in the Anglo-French Library of Medical and Biological Science. In 1913 Gibson put forward the suggestion that certain forms of splenomegaly included in the terms splenic anemia and Banti's disease were the result of an invasion of the spleen by a form of streptothrix, which, he thought, could be demonstrated in the pigmented nodules found in these cases scattered throughout the substance of the spleen. A further study of these has strengthened him in this opinion that they are the cause of the disease, and that a mycelial origin is the only possible explanation of the threads that were described. With these two diseases he now includes acholuric jaundice. The pigmented nodules known as the Gandy-Gamma nodules, from the descriptions by these two workers in 1905 and 1923-4, contain mycelial-like structures staining slate blue with hematoxylin and giving a feeble iron reaction. They do not stain with Weigert's fibrin stain, they are Gram-negative and give no reaction with Van Gieson's stain. Gibson regards these as streptothrix mycelia. In 1925 Nanta and associates found similar bodies in the spleens of cases of splenic anemia which they have interpreted as the mycelia of a fungus belonging to the genus *aspergillus*. The mycelial nature of the fibers found in the Gandy-Gamna nodule has not been generally accepted. Langeron believes that the supposed mycelia are fibers of fibrin impregnated with iron. Gibson's book is a resumé of his findings and views, with a consideration of those of Nanta, and the criticisms of Langeron. The question of the nature of the Gandy-Gamna nodule and its peculiar inclusions remains unsettled, and the problem can only be settled by the repetition of these observations by numbers of other workers.

*The Chest* By L. R. SANTI, M.D., F.A.C.P., Professor of Radiology and Director of Department, St. Louis University Medical School. Radiologist to the University Group of Hospitals. *Annals of Roentgenology. A Series of Monographic Atlases.* Edited by James T. Case, M.D.,

Volume Eleven, 561 pages, 376 roentgen-ray studies and 153 clinical illustrations. Paul B. Hoeber, Inc., New York, 1930. Price \$20.00.

The increasing importance of the x-ray examination in the diagnosis of morbid conditions of the chest make a knowledge of the interpretation of films of the chest both desirable and necessary, even imperative. It cannot be expected that the general practitioner will become expert in such interpretation, but he should have sufficient knowledge of this relatively new field of diagnostic aid to understand the general significance of chest films, to be able to follow their expert interpretation with understanding and to acquire a practical acquaintance with the principles of x-ray interpretation. Physical diagnosis has been tremendously enriched by the application of x-ray examinations to the study of diseases of the chest, it is as essential that the physician of today add a practical knowledge of the principles underlying such examinations, as it is for him to acquire a knowledge of auscultation and percussion. In fact, the writer believes that it is the practitioner who should acquire expert knowledge in the interpretation of x-ray films, in order that he may supplement and check up the knowledge gained by other methods of physical diagnosis. If he depends upon the roentgenologist alone, who usually does not possess a knowledge of other methods of physical diagnosis, there is the danger that he may come to rely too much upon the x-ray film, or even, as is actually the case with some busy practitioners, come to depend upon it alone, to the neglect of the older methods of physical diagnosis. For the practitioner must constantly have in mind the fact that the x-ray film does not tell the whole story of pulmonary disease; there are morbid conditions of the chest not revealed by roentgenological examination. This makes it all the more imperative that the practitioner should at least have a fairly good working knowledge of the interpretation of films. This volume is undertaken for this very purpose, to give a mutual exchange of knowledge for the aid of the clinician. It will also serve as a compilation for the guidance of roentgenologists.

ologists The book is divided into three parts Part I dealing with certain considerations essential preliminary to undertaking chest interpretations, Part II dealing with the evidences of pathology as they appear at roentgenological examination, enumerating all conditions affecting each lung structure and showing as far as possible where in their roentgenological appearance differs in each case; Part III given over to a detailed consideration of each disease, following it through from inception to termination In this way, in any roentgenogram of the chest, Part II serves to establish within a few possibilities the identity of a pathological lesion, while Part III completes the differentiation by a detailed account of each

possibility established. The material of this book is very complete; the arrangement excellent; and the discussion full and to the point. The illustrations have been beautifully accomplished, each one tells its story clearly and plainly There is not one single poor one in the book. The volume offers a tremendous aid to the study and diagnosis of chest diseases; and is an essential to the armamentarium of the practicing physician. The book is beautifully gotten up, it is a work of art, reflecting the greatest credit upon the firm of Hoeber. It marks a decided step forward in the study and diagnosis of morbid conditions of the chest

## College News Notes

### JOHN PHILLIPS MEMORIAL PRIZE

A large number of entries have been made in competition for the 1931 award of the John Phillips Memorial Prize. The submission of dissertations and theses closed on August 31, but it is probable that the Board of Regents of the American College of Physicians will offer the prize of \$1500.00 for 1932, as well as for 1931.

Announcement of the winning thesis will be made at least two months in advance of the Baltimore Clinical Session, March 23-27, 1931.

At the Detroit, 1930, Session of the American Medical Association, Dr. Frank Smithies (Master), Chicago, was elected by the House of Delegates, a member of the Council of Scientific Assembly to serve for a period of five years.

Dr. Meldrum K. Wylder (Fellow), Albuquerque, N. M., read a paper on "The Preventive Measures in Pediatrics" before the last meeting of the New Mexico State Medical Association.

At the Detroit Session of the American Medical Association, the following Fellows from Georgia participated in the program.

Dr. W. R. Houston, Augusta, as Vice Chairman of the Section on the Practice of Medicine.

Dr. James E. Paullin, Atlanta, as a member of the Executive Committee of the Section on the Practice of Medicine.

Dr. Stewart R. Roberts, Atlanta, read a paper on "Agranulocytic Angina" before the Section on the Practice of Medicine.

Dr. E. C. Thrash, Atlanta, a delegate from Georgia served as Chairman of the Reference Committee on Amendments to the Constitution and By-Laws of the House of Delegates.

Dr. Allen H. Bruce, Atlanta, as a member of the Board of Trustees.

At the last session of the American Medical Association held at Detroit, Mich., Dr. Samuel Weiss read a paper on and demonstrated a new gastroscope. He also had a booth in the scientific exhibit where models and charts for teaching gastroenterology were shown. The main feature was a phantom stomach with numerous cuts fitting into it showing normal and pathological conditions of the gastric mucosa. This model is the only one in existence at the present time, and was favorably commented upon by those who viewed it.

Dr. Edgar Erskine Hume (Fellow), M. C., U. S. A., received the honorary degree of Doctor of Laws from the University of Kentucky on June 2, 1930.

Dr. Warren Pearce (Fellow) with Dr. R. A. Harris, Quincy, Ill., is the author of an article entitled "Lead Poisoning. With An Analysis of Employees of an Enameling Plant" in the July Issue of the Quincy Medical Bulletin.

Dr. Alfred Meyer (Fellow), New York, N. Y., has been engaged in research work at Woods Hole, Mass., during the summer months. Each year, teachers in all branches—biology, physics, zoology, physiology, botany, medicine, anthropology, chemistry and subdivisions—assemble there for all sorts of study and research in their respective lines. Excavations have been begun for an oceanographic institute to be run by a separate Board of Trustees from the Marine Biological Laboratory.

Dr. G. H. Wells (Fellow), Philadelphia, President of the National



mann Hospital, is the author of an article, "Digitalis. Relative Efficiency and Stability of the Various Preparations of Digitalis", which appeared in the July Number of the Hahnemannian Monthly.

Dr William W Cadbury (Fellow), Canton, China, was elected Superintendent of the Canton Hospital during June. This hospital has now been transferred to Lingnan University, and is the first hospital to be established in China along western lines. It has been engaged in active service for nearly ninety years.

Dr Crawford R Green (Fellow), Troy, N. Y., is author of the contributed article for July in the Hahnemannian Monthly, "Leaves from a Therapeutic Note-book". The original paper was read on April 22, 1930, before the Homeopathic Medical Society of the State of New York, at Brooklyn.

Dr. Clarence R Bell (Fellow) of the Medical Corps of the U S Army, is now on duty at the Sternberg General Hospital, Manila, P. I., as Chief of the Medical Service, where he relieved Dr Luther R Poust (Fellow), Major, M C, U S A, who has been transferred to another station.

Dr Williams S McCann (Fellow) and Dr John R Williams (Fellow), Rochester, N Y, were recently appointed examiners in medicine by the National Board of Medical Examiners.

Dr. J. A Myers (Fellow), Minneapolis, is the author of a new book entitled "Tuberculosis Among Children", published by Charles C. Thomas, Springfield, Ill.

Dr Frederick J Farnell (Fellow), Providence, R. I., is the author of a series of articles on modern aspects of social work covering "The Feeble-Minded", "The Mentally Diseased", "The Delinquent and the Criminal", with a special introduction and conclusion in the Evening Bulletin of Providence during July.

Dr. Carl V. Vischer (Fellow), Philadelphia, Assistant Physician to the Hahnemann Hospital, held a special Medical Clinic on "Pulmonary Tuberculosis" at the hospital on May 1. There were lantern slide illustrations, and the entire clinic was published in the July Issue of the Hahnemannian Monthly.

Dr August S Ketch (Fellow), Altoona, Pa., was the author of an article entitled "Electrocardiogram of Dextrocardia" in the July Issue of the Pennsylvania Medical Journal.

Dr Jesse L Lenker (Fellow), Harrisburg, Pa., after touring France and Germany during the summer, attended the International Hygiene Exhibit and World Health Conference in Dresden, Germany.

Dr Arthur W White (Fellow), Oklahoma City, Okla., contributed an article entitled "Amebiasis—Present Day Interest" to the July Issue of the Journal of the Oklahoma State Medical Association.

Dr Everett S Lain (Fellow), Oklahoma City, Okla., has visited various European centers during the summer, and attended the International Dermatological Association's meeting at Oslo, Norway.

Dr Henry M Moses (Fellow), Brooklyn, and Dr Joseph G Terrence (Associate), Brooklyn, returned about August 1 from the Tour of the Thermal Resorts of France at the invitation of the French Government. At the close of the official tour, they visited hospitals and physicians on tour through Switzerland, Italy, Austria, Germany and England.

Dr Ray M Balyeat (Fellow), Oklahoma City, with Dr Fannie L Brittain, is author of an article on "Allergic Migraine Based on the Study of Fifty-five Cases" in the August Issue of the American Journal of the Medical Sciences. In the same issue, Dr I I Lemann (Fellow), New Orleans, is author of the article on "The Futility of Alkali Treatment in Diabetic Coma. Analysis of Forty-seven Cases."

In the August Issue of the Southern Medical Journal, the following articles by Fellows of the College appeared

Dr Sinclair Luton (Fellow), St. Louis,  
"Comparison of Methods Used for Estimating the Size of the Heart"

Dr C S Holbrook (Fellow), New Orleans,

"Encephalitis and Encephalomyelitis Following Vaccination Against Smallpox Report of Five Cases"

Dr Oliver C Melson (Fellow), Little Rock,

"Limits of Normal From a Clinician's Point of View"

Dr Claude L Holland (Fellow), Fairmont, W Va, pursued postgraduate study in Pediatrics at the Harvard Medical School during the summer.

Dr Alfred Gordon (Fellow), Philadelphia, is the author of "The Problem of Neoarsphenamine-Resistance and Neoarsphenamine-Intolerance (Hypersensitivity) in Neurosyphilis" in the July Issue of the Journal of Chemotherapy

In the August Issue of Radiology, the following Fellows contributed the articles indicated

Dr Preston M Hickey, Ann Arbor, Mich,

"Economic Problems of the X-Ray Laboratory"

Dr Arthur C Christie, Washington, D C,

"The Work of the Committee on the Cost of Medical Care"

Dr Harold Swanberg, Quincy, Ill,

"The Pre-Radium Treatment of Carcinoma of the Uterine Cervix"

Dr Alden Williams, Grand Rapids, Mich,

"New Experiments on Cancer Cure"

Dr Preston M Hickey (Fellow), Ann Arbor, Mich, was the recipient of the degree of Doctor of Science at the June graduation of the Detroit College of Medicine and Surgery.

Dr Edwin W Gehring (Fellow), Portland, Maine, presented a paper on John Hunter entitled "A Great Scotsman and His

Brother" at the Aroostook (Maine) County Medical Society, recently

Dr Eugene H Drake (Fellow), Portland, Maine, conducted a clinical conference on the heart, and Dr Elton R Blaisdell (Fellow), Portland, Maine, conducted a similar conference on diabetes and nephritis at the Maine General Hospital, June 2.

Dr. Thurman D Kitchin (Fellow), Wake Forest, N C, who has been Dean of the Medical School at Wake Forest for thirteen years and who is a past President of the Medical Society of the State of North Carolina, has been elected President of Wake Forest College

Dr John B Youmans (Fellow) has been appointed Associate Professor of Medicine and also Director of graduate instruction on the medical faculty of Vanderbilt University, Nashville, Tenn

Dr Hubert Work (Fellow), Denver, Colo, spoke on the subject, "The Doctor in Politics," at the annual meeting of the Colorado State Medical Society at Pueblo, September 9-11

Dr Constantine F Kemper (Fellow), Denver, Colo., addressed the San Luis Valley Medical Society at Monte Vista (Colo), June 21

Dr James H Hutton (Associate), as President of the Chicago Medical Society, has named a Committee to aid in the survey of Illinois hospitals for the mentally diseased. Among those named on the Committee are Dr Robert S Berghoff (Fellow) and Dr. George W Hall (Fellow), both of Chicago

Dr Philip S Hench (Fellow), Rochester, Minn., addressed the Jefferson County (Ohio) Medical Society during the summer on "Rheumatic Diseases and Gout—Their Differential Diagnosis and Treatment"

Dr. Archibald H Beard (Fellow), Minneapolis, Minn., addressed the Barton-Pull-Washburn-Sawyer-Burnett County Medical

Society at its June meeting on "Diabetes Mellitus and Vascular Disease."

Dr. Ray C. Blankinship (Fellow), Madison, Wis., addressed the Marinette-Florence County (Wisconsin) Medical Society, recently, on "Medical Management of Peptic Ulcers"

Dr. Laurence R. DeBuys (Fellow), New Orleans, was elected President-Elect of the American Pediatric Society on June 17

Dr. David Riesman (Fellow), Philadelphia, addressed the Sixth Clinical Congress of the Connecticut State Medical Society at New Haven, September 16-19, on "Blood Pressure"

Dr. William E. Gardner (Fellow), Louisville, Ky., delivered a paper on "Some Inflammatory and Degenerative Conditions of the Central Nervous System Due to Specific Infection" before the Third District (Kentucky) Medical Society's meeting, July 9

Dr. Warfield T. Longcope (Fellow), Baltimore, Md., was a guest speaker at the annual meeting of the Minnesota State Medical Association at Duluth, July 14-16

Dr. Louis Faugeres Bishop (Fellow), New York, N. Y., addressed the Lake Keuka Medical and Surgical Association, comprised of twenty-two counties of western and central New York, at Lake Keuka, July 10-11, on "Analysis of One Hundred Cases of Cardiac Pain, as Seen in Office Practice"

Dr. Charles F. Martin (Master), Montreal, Que., will address the third annual graduate fortnight of the New York Academy of Medicine, October 20-21, on "Continued Education of the Practitioner"

Dr. Ernest E. Irons (Fellow), Chicago, Ill., will also deliver a paper on "Facts and Fancies Concerning Vaccines and Nonspecific Therapy"

Dr. John P. Munroe (Fellow) and Dr. Archibald A. Barron (Fellow), with Dr. William Allan, all of Charlotte, N. C., discussed the subject of pellagra at the summer meeting of the York County Medical Society

Dr. Henry Boswell (Fellow), Sanatorium, Miss., was one of the scheduled speakers at the state conference on tuberculosis, held at Salisbury, N. C., August 7, of the North Carolina Tuberculosis Association

Dr. Thomas Klein (Fellow), Philadelphia, Pa., has been appointed Professor of Applied Therapeutics on the faculty of the Temple University School of Medicine

Dr. Waller S. Leathers (Fellow), Nashville, Tenn., has been elected President of the National Board of Medical Examiners

Dr. J. Gurney Aaylor (Fellow), Milwaukee, was elected a member of the National Board of Medical Examiners, representing the Wisconsin State Board of Medical Examiners

Dr. Charles A. Elliott (Fellow), Chicago, Dr. William DeB. MacNider (Fellow), (Chapel Hill, N. C., and Dr. Walter W. Palmer (Fellow), New York City, were elected members of the Board at large. The Constitution has been amended so as to increase the membership from twenty-one to twenty-seven. This was necessitated by a ten per cent increase in the number taking examinations during the present year as compared with the previous year. Forty states, in addition to the territories of Hawaii, Porto Rico and the Canal Zone, now recognize the national certificate. England, Scotland, Ireland and Spain give partial recognition to the Board's examinations.

Dr. Adolph Sachs (Fellow) with Dr. Raymond L. Traynor, of Omaha, Nebr., is author of an article entitled "Ulcerative Colitis—With Special Reference to Diet" in the August Issue of the Nebraska State Medical Journal

Dr. Floyd Clarke (Fellow), Omaha, is author of an article entitled "Acrodynia

With Report of Three Cases" in the same issue of the above journal

Acknowledgment is made of the receipt of the following reprints of publications by members of the College, which have been indexed and added to the College Library

Dr Samuel Ayres, Jr (Fellow), Los Angeles, Calif

"Gastric Secretion in Psoriasis, Eczema and Dermatitis Herpetiformis"

"Pityriasis Folliculorum (Demodex)"

"Eczema—Some Recent Contributions to its Study"

Dr Miles J Breuer (Fellow), Lincoln, Nebr

"The Treatment of the 'Early' Case of Tuberculosis"

"Tuberculosis The Nature of the Diagnostic Problem"

Dr Carl R Howson (Fellow), Los Angeles, Calif

"Climate In Pulmonary Tuberculosis"

"Heliotherapy in Pulmonary Tuberculosis—Its Possibilities and Dangers"

"Explaining Artificial Pneumothorax to the Patient"

"Standardization in Artificial Pneumothorax"

Dr E A Sharp (Fellow), Detroit, Mich

"An Antianemic Factor in Desiccated Stomach"

"Acute Influenzal Infection—An Interpretation of Mild Respiratory Diseases"

Dr George L Waldbott (Associate), Detroit, Mich

"Hypertension Associated with Allergy"

## OBITUARY

Dr. Robert Hall Babcock (Fellow), Chicago, Ill., died, June 28, at Green Lake, Wis., of heart disease, aged 79

Dr Babcock was born at Watertown, New York, received his A.B. and A.M. degree from Western Reserve University, his medical degree from the Chicago Medical College, 1878, and also from the Medical Department of Columbia College, New York City, in 1879. He was awarded the honorary degree of LL.D. from the University of Michigan in 1910. His practice had been devoted to Internal Medicine since 1883. From 1891 to 1905, he was Professor of Clinical Medicine and Diseases of the Chest at the College of Physicians and Surgeons, Chicago, and Attending Physician to Cook County Hospital. He was Professor of Clinical Medicine and Physical Diagnosis at the Chicago Postgraduate Medical School from 189 to 1896. In later years, he was Consulting Physician to the Passavant Hospital and a member of the associate staff of the St. Luke's Hospital.

Dr Babcock was President of the Chicago Tuberculosis Institute from 1916 to 1921, President of the American Medical Association, 1901, President of the Mississippi Valley Medical Association, 1911; a Fellow of the American College of Physicians since 1916. He was a member of the American Congress of Physicians and Sur-

geons, the National Tuberculosis Association, Institute of Medicine of Chicago, Chicago Society of Internal Medicine, American Climatological and Clinical Association, National Association for Study and Prevention of Tuberculosis, Tri-State Medical Society, emeritus member of the Association of American Physicians, honorary member of the Edinburgh Medico-Chirurgical Society, member of the University Club, Chicago, Delta Kappa Epsilon Fraternity and the Delta Kappa Epsilon Club of New York City. He was the author of several books, among them "Diseases of the Heart and Arterial System," "Diseases of the Lungs" and "Your Heart and How to Take Care of it."

Dr Babcock was among the earliest members of the College, was a regular attendant at its Annual Clinical Sessions and exerted a wholesome influence on the development of its ideals and purposes

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Dr. Nicholas Lukin (Associate), New York, N. Y., died June 10, 1930, aged 60 years. Dr. Lukin graduated from the University and Bellevue Medical College in 1908. He was Chief of the Clinic, and Adjunct, Department of Internal Medicine, of the Bronx Hospital, and Cardiologist to the Bronx Maternity Hospital

# The Indications for and the Results of Artificial Pneumothorax Treatment in Pulmonary Tuberculosis\*†

By J BURNS AMBERSON, JR

**P**ULMONARY tuberculosis, recognized and treated properly in its very early stages, especially before softening and excavation have occurred, is a very healable disease. The problem of treatment would be relatively simple if it could be instituted always in this early most favorable stage. But the fact is that at least seventy-five per cent of tuberculous patients are in the moderately advanced or far advanced stage of the disease before they are correctly diagnosed and persuaded that treatment is necessary. Actually, therefore, one of our chief responsibilities is the care of advanced cases.

Once the minimal or early stage of pulmonary tuberculosis has passed and the disease has progressed to the point of necrosis and cavity formation treatment becomes much more difficult and complicated. Many of these patients do remarkably well on sanatorium rest treatment—striking healing by resolution and fibrosis is sometimes ob-

seived, cavities not exceeding 2 to 3 cm in diameter become obliterated in approximately fifteen to twenty per cent of the cases, and larger ones occasionally close if other conditions are favorable. But, even so, a considerable percentage of this more advanced group do not respond and are prone to relapse, and during their tenure of life which may be years, many of them are chronic invalids. For these we look for some artificial aid.

It would be unfortunate indeed, if, in their enthusiasm for the efficacy of newer aids to recovery physicians forgot the fundamental value of rest treatment. Pneumothorax and surgery are accomplishing remarkable things when the usual measures do not suffice but let it be remembered that Nature when given free sway with the patient at intelligently regulated rest has even more remarkable things to her credit. If healing can be completed by Nature alone—as it often is—the finished

monary tuberculosis, as well as in its unfavorable evolution, is fundamental to a consideration of prognosis and treatment. The following are important in considering the use of artificial pneumothorax.

Once established in the lung, chronic tuberculosis of adults spreads by two chief ways. The first is direct extension to adjacent parts of the lung. The second is by contamination of distant or nearby tissues through tubercle-bacillus-laden pus. By this latter way, the bacillus is often carried through the bronchi to other parts of the same lung or to the opposite lung, and new (bronchogenic) foci of disease are set up. Similar surface contaminations of the mucous membranes of the larynx and intestine are chiefly responsible for the two most frequent complications of pulmonary tuberculosis, namely, tuberculous laryngitis and intestinal tuberculosis. There are other modes of spread, but these two confront us most often.

The discharge of infectious pus (a positive sputum) in ninety-five per cent or more of these cases is from a pulmonary cavity. The potential menace of the cavity is apparent for this as well as other reasons, such as the possibility of hemorrhage. Actual follow-up records at the Loomis Sanatorium show that tuberculous patients who never had a cavity or a positive sputum live longest and are least disabled of any patients with cavities which closed under treatment and whose positive sputum became negative have the next best chance, those whose cavities remain open in spite of treatment and whose sputum continues

positive have the poorest prospect of living long and, while living, the poorest prospect of being able to lead a normal working life.

The chief aim of treatment is to bar any further spread of the disease, which means to promote the maximum of healing by resolution and fibrosis and to bring about closure of discharging cavities, and then to maintain this state until the healing is most likely to remain durable and lasting. Loss of constitutional symptoms, such as fever, gain in body weight and other outward signs of improvement are to be sought, but these signs alone may be very deceptive as indicators of the ultimate safety and chance of lasting recovery of the patient. We must be sure, in addition, that we have secured satisfactory intrinsic healing of the disease if we are to avert later spreads, complications and chronic disability.

It is in the group of patients who do not achieve, or cannot be expected to achieve, the maximum healing and symptomatic recovery under approved rest treatment within a reasonable period of time that we consider the possibilities of artificial collapse therapy, of which the most extensively used form is artificial pneumothorax. In surveying this group, with pneumothorax in mind, we eliminate at once as unsuitable for such treatment all cases of advanced excavating disease widely affecting both lungs. Likewise we exclude provisionally those patients in whom tuberculous complications or nontuberculous disease appear to be of fatal omen and those who are obviously in the terminal stages of pulmonary tuberculosis. In unilateral

cases of the last type, pneumothorax is often attempted but usually with poor results, it is justifiable if clearly understood to be a desperate last resort measure

The cases most suitable for pneumothorax may be listed as follows

1 Extensive tuberculosis in one lung with widespread caseation and large single or multiple cavities. Usually the sputum is considerable and constitutional symptoms are very evident. These cases seldom heal sufficiently on simple rest treatment and pneumothorax should be induced after a short period of observation

2 Acute unilateral pneumonic phthisis requires prompt action. In such cases if the toxemia is profound, the tuberculous process may caseate and break down in a few weeks, at which time pneumothorax may be ineffective, whereas in the first week or two it may save the day. If symptoms are mild, it is justifiable to wait and watch carefully with frequent X-ray films to determine the trend of the disease

3 More chronic unilateral cases in which the patient's general resistance is good and in which there is a tendency to fibrosis but in which cavities 5 cm. or more in diameter are already present. Usually a period of observation of a few weeks or months shows that these cavities will not close. Pneumothorax is given, not so much to control immediate symptoms but more to avert a spread of the disease and to restore the patient to working ability

4 Hemorrhage cases often need immediate pneumothorax. Almost all pulmonary hemorrhages in tubercu-

losis come from cavities. If the lung can be collapsed, the hemorrhage is stopped and the cavity is closed. Bleeding may be controlled even though the cavity remains partially open. In any bleeding case, intractable by other means, pneumothorax should be considered and usually is given at once. If it is a unilateral cavity case, one should not wait too long, even though the bleeding is not severe, because a posthemorrhagic spread of the disease is most to be feared

5 In addition there are many cases in which indications are provisional and not so definite. In fact, most patients are best tried for a time on ordinary rest treatment to test their response and their powers of resistance. Then, if the disease proves progressive in one lung, as shown by careful clinical, laboratory and X-ray observation, pneumothorax is given. In some cases a few weeks decides this, in others, the issue may be in the balance for months. In recent years we have gathered courage to proceed earlier with pneumothorax in these patients with a doubtful prognosis, because, otherwise we often do no more than prolong their lives for years of chronic invalidism

6 The most difficult for decision are those cases in which the better lung is also diseased or in which other complications exist. Healed but not tuberculous deposits in the better lung should not weigh heavily against pneumothorax. Small fresh infiltrates in this lung often lead to pneumothorax is given on the weaker side, if the rest is proper. If the rest



other comparable situations, no written rule is an adequate guide. Rules are compromised, and the clinical judgment of the physician experienced in this work as well as the attitude of the patient determines the line of action. In a few cases of bilateral disease, pneumothorax may even be given simultaneously on both sides.

The actual technique of giving pneumothorax and of managing these cases is a matter of accessible record. One important principle should be emphasized, which is that rest treatment is absolutely necessary in every case during the early months of pneumothorax. Later, it is often possible for the patient to resume work, meanwhile continuing his treatment. The technique of inducing pneumothorax is simple, and the needed skill is in knowing how to handle the various difficulties that are frequently encountered. They include pleural adhesions wholly or partially preventing the proper collapse of the lung, effusions usually of a serous character, empyema in a very few cases, air embolism rarely, and other minor complications. The judgment of the surgeon often is needed when pneumothorax fails.

The action of pneumothorax is dependent on a number of factors which have been substantiated clinically, pathologically and experimentally. They are chiefly immobilization of the lung in a more or less collapsed and functionless state, closure of cavities with later permanent obliteration of their lumina and stoppage of the infectious discharge (sputum); alteration of the circulation of the blood in

the treated lung, and lymph stasis in this lung.

The experience with pneumothorax treatment at the Loomis Sanatorium, as recorded by Peters,<sup>1</sup> yields very convincing evidence of the efficacy of this measure. He compared the ultimate fates of those patients in whom pneumothorax was indicated but could not be given, and of those in whom pneumothorax was given satisfactorily. As compared with the former group, three times as many of the latter were alive after two to fourteen years, and, of those living, three times as many were leading normal, useful lives. Recently Riggs and I have studied the Loomis Sanatorium cases in which pneumothorax treatment has been completed with subsequent re-expansion of the lung. We have 165 of these cases, followed for an average period of five years after re-expansion. In 89 healing was good and the cavities were permanently closed, 78 (87.6 per cent) of these are living, and 78.2 per cent of the living are able to work or lead normal lives. In 76 healing was incomplete, and in none of these were the excavations completely closed on re-expansion, only 35 (41.6 per cent) of these are living, and, of those living, only 48.6 per cent are able to live normally, 4 of these having had later surgical treatment. Comparisons such as these speak for themselves and bear out our general belief that pneumothorax when it collapses the lung ade-

<sup>1</sup>PETERS, A. Artificial Pneumothorax at the Loomis Sanatorium over Fourteen Years. *Amer Rev Tuberc*, 1928, xii, 348.

quately and is continued long enough, restores a majority of the patients selected who otherwise would be destined for an early death or, at best, permanent disability

The problem of the necessary duration of artificial pneumothorax has been a vexing one, on which our study of re-expanded cases has thrown some light. We have found that the total duration of treatment is not so important as the duration of treatment after the cavities have been closed and the sputum has become negative for tubercle bacilli. Depending on a num-

ber of variables such as the original state of the lesion and size of the excavation, our patients did very well after re-expansion, if the lung was satisfactorily collapsed and the cavities kept closed for from eighteen months to two years. Often it takes months to close cavities, so that the average total length of treatment in our most successful cases was from two to three years. With close observation and care it is not necessary to continue pneumothorax indefinitely, once a satisfactory collapse has been obtained.

# Phrenicectomy and Intercostal Neurectomy for Pulmonary Tuberculosis\*†

By JOHN ALEXANDER, M A , M D , F A C S

**S**ATISFACTORY results from the use of surgery in certain of those cases of pulmonary tuberculosis which have failed to do well under sanatorium régime have been sufficiently numerous to create a demand for extension of the classical indications. This demand is being met. A few new procedures are being introduced, the effects of the old ones are now better understood, operative technique is being constantly improved and combinations of various procedures are being applied to a steadily widening variety of cases.

Unilateral diaphragmatic paralysis is being used more frequently than ever for both restricted and extensive lesions in either the upper or lower portion of the lung. In certain cases it is of surprising symptomatic value for pain that is caused by the tug of a moving diaphragm upon diaphragmatic adhesions and for excessive coughing or vomiting or dyspnea that is due to the same cause.

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\*Part of a symposium on "The Surgery of Pulmonary Tuberculosis" presented by invitation before the 14th annual meeting of the American College of Physicians at Minneapolis, February 14, 1930.

†From the Department of Surgery (Division of Thoracic Surgery), University of Michigan Medical School.

An increasing number of clinicians now prefer diaphragmatic paralysis to pneumothorax for unilateral lesions that do not include cavities of such large size that phrenicectomy could not be expected to close them. Reasons for this preference are that complications from expertly performed operations on the phrenic nerve are fewer than those which occur with artificial pneumothorax and that a single minor operation under local anesthesia takes the place of repeated refills of the pneumothorax with air for one, two, three or more years. If pneumothorax should later prove necessary the presence of diaphragmatic paralysis is usually useful rather than harmful.

Complete paralysis of half of the diaphragm can be made temporary, lasting about five months, if the main phrenic nerve as well as all accessory nerves are merely crushed instead of resected.

Since diaphragmatic paralysis can thus be made revocable its indications are obviously widened. When a patient who has failed to benefit from sanatorium régime has tuberculosis of both lungs and when it seems that more active measures offer even a small chance of improvement or cure, a logical procedure that J. Burns Am-

berson<sup>5</sup> has proposed and that John Barnwell and I have used, is first to attempt to induce pneumothorax on the worse side before performing phrenicectomy on either side. If successful, another pneumothorax, a partial one, may be attempted on the other side or a temporary interruption of the phrenic nerve performed. If, however, satisfactory pneumothorax should fail to be induced on the first or worse side, a permanent phrenicectomy should be used there and later, perhaps, a partial pneumothorax attempted on the other side. Total paralysis of both sides of the diaphragm has not yet been shown to be effective or constantly safe. The principle of proceeding as described in this paragraph is to reserve the phrenic nerve operation for that side which is unable, on account of adhesions, to accept a pneumothorax.

Return of function in a temporarily paralyzed diaphragm begins with short descending movements during quiet inspiration but the paradoxical movements persist on inspiratory sniffing, and the high position of the diaphragm still exists at this stage.

My experience with diaphragmatic paralysis has not led me to the conclusion that it is responsible, except perhaps rarely, for activation of tuberculous lesions in the contralateral lung. Tuberculous disease certainly does often progress in the contralateral lung after phrenicectomy, but I believe that it does so at least as frequently in patients with similar lesions in which no operation whatever has been performed. For this reason temporary phrenic nerve interruption in contradistinction to permanent interruption (phrenicectomy) is not often used except for the indications discussed in the preceding paragraphs.

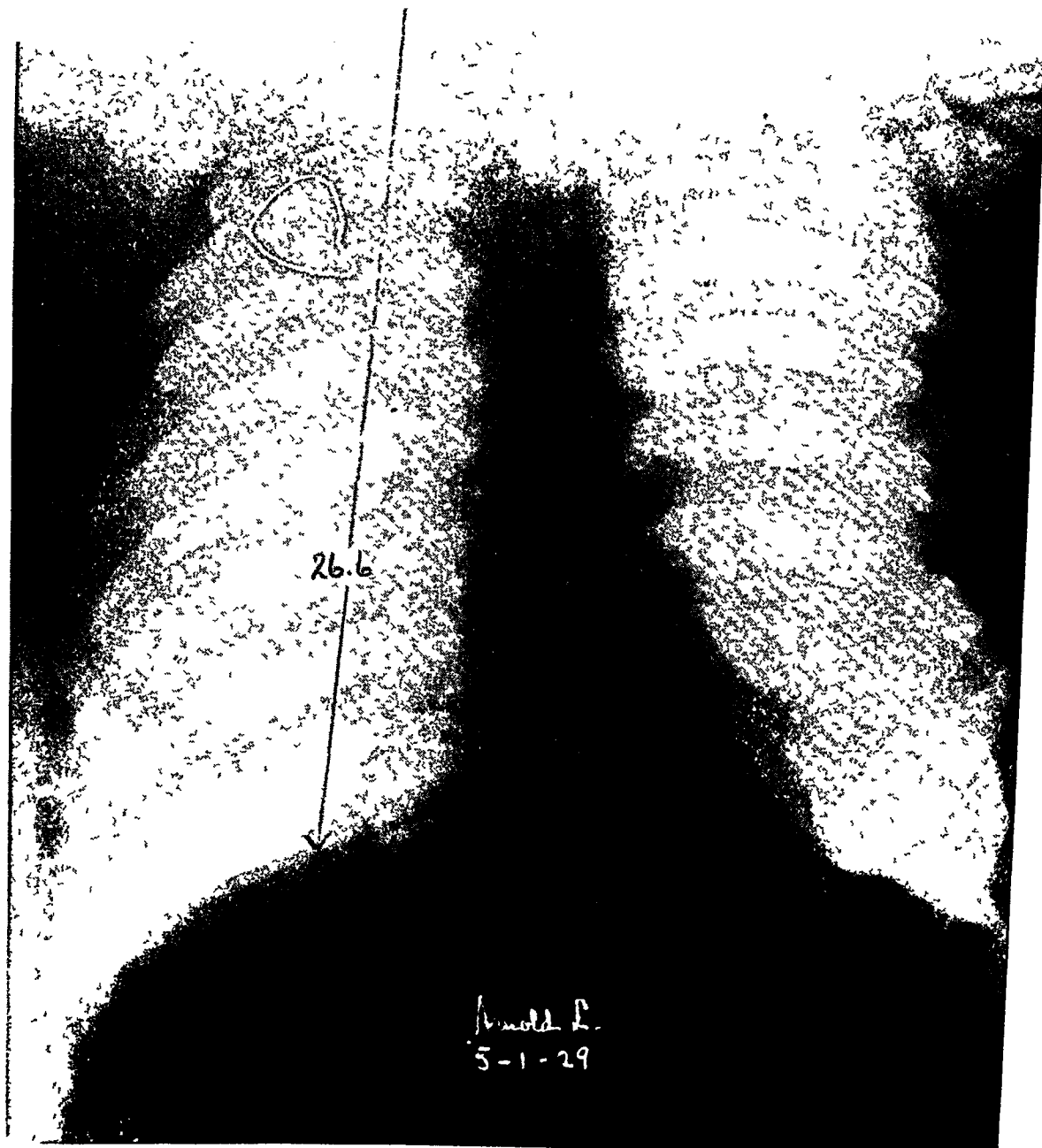


FIG 1 Tuberculous cavity outlined with pencil, of at least 12 months duration  
Sputum averaged 70 cc daily See Fig 2 Patient referred by Dr Salvatore Locojano,  
Marquette, Michigan

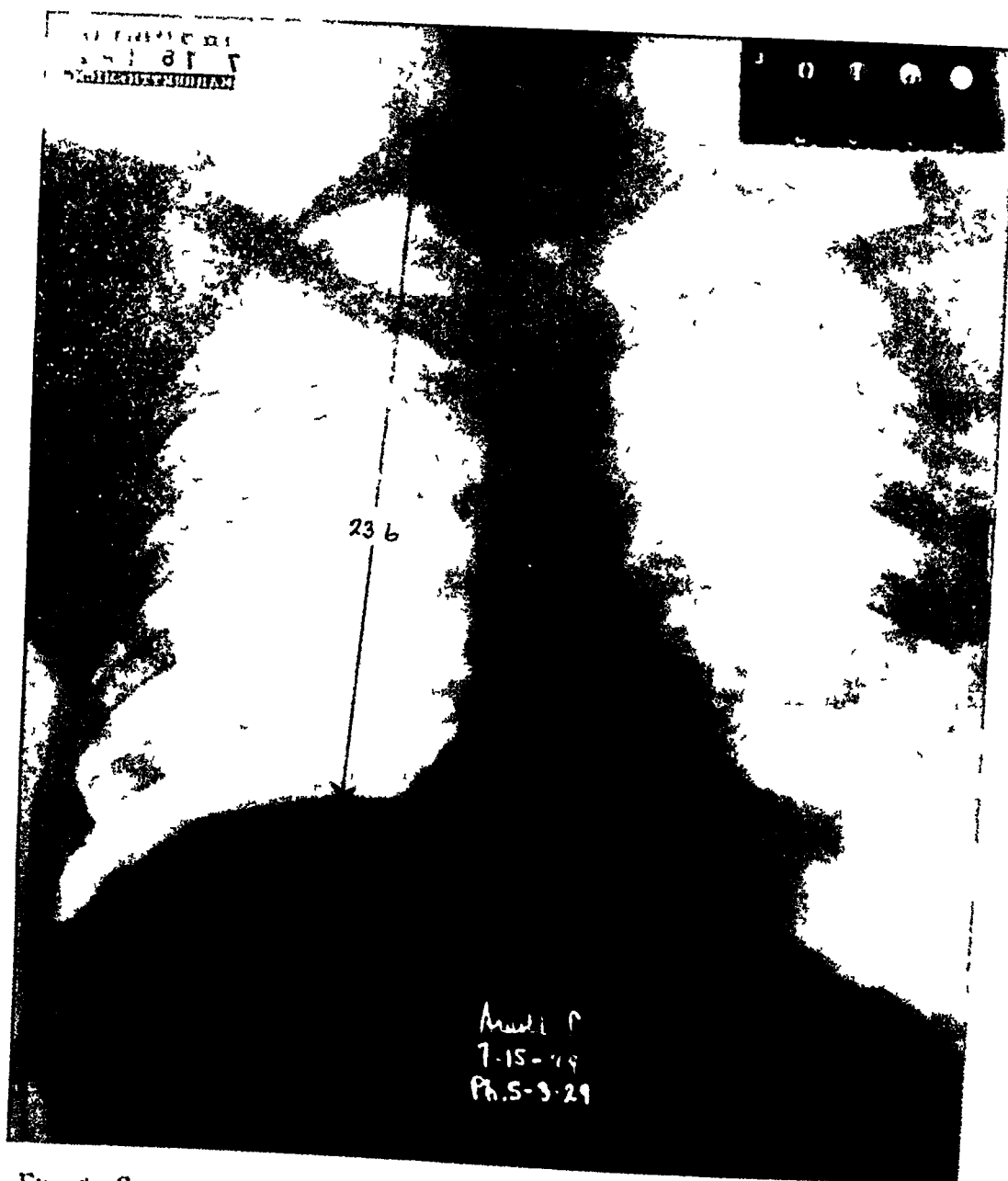


FIG. 2. Same patient as in Fig. 1. Complete closure of cavity and disappearance of sputum ten weeks after phrenicectomy, which resulted in only moderate rise of vertical distance between first thoracic transverse process and dome of diaphragm. The clavicle is unsuitable as a measuring point because of its variable position in different films and the distance between the tops of the hemidiaphragms is not strictly comparable in comparison between different films because of the present technique of the separated hemidiaphragm during different roentgen exposures.

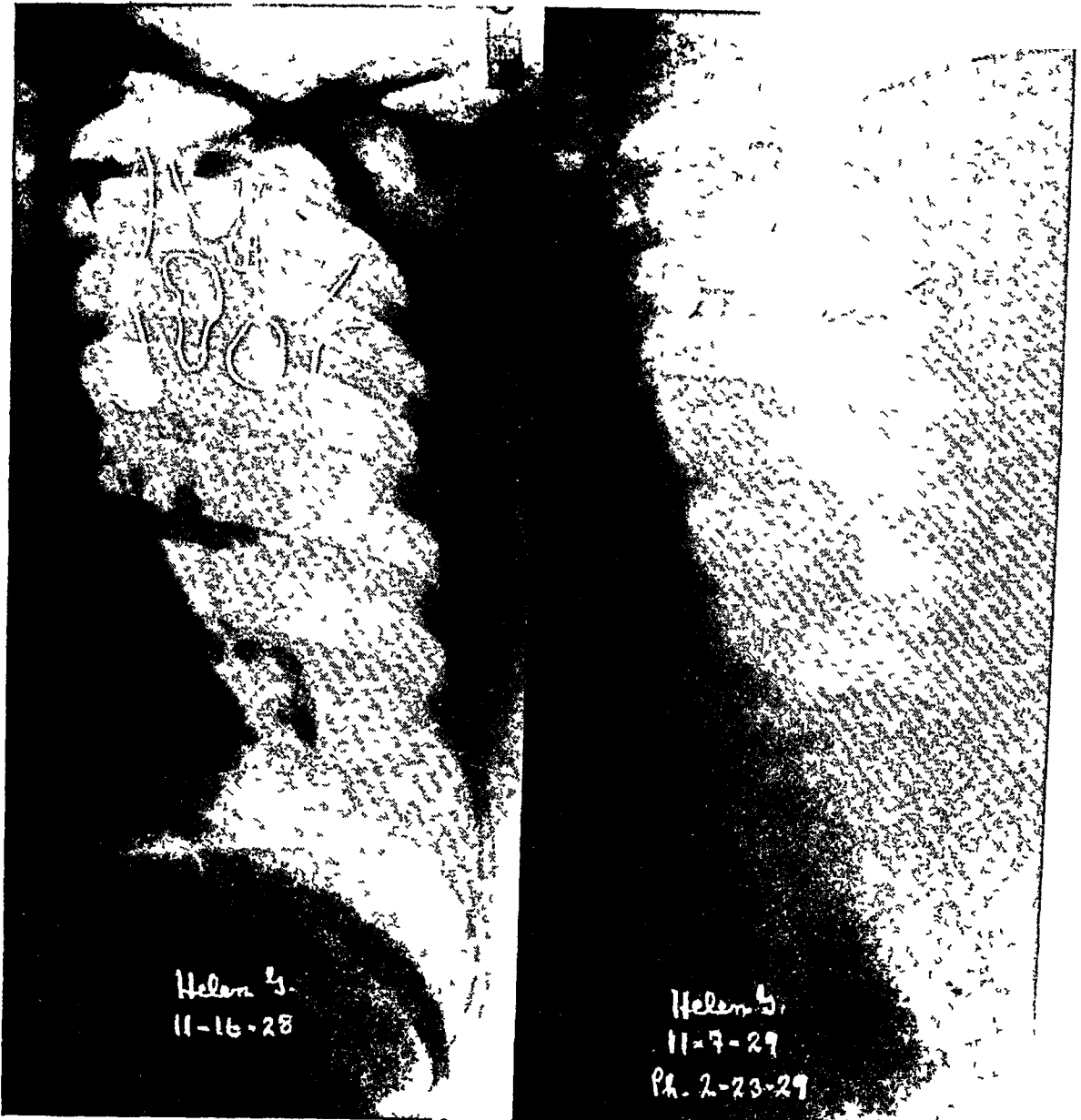
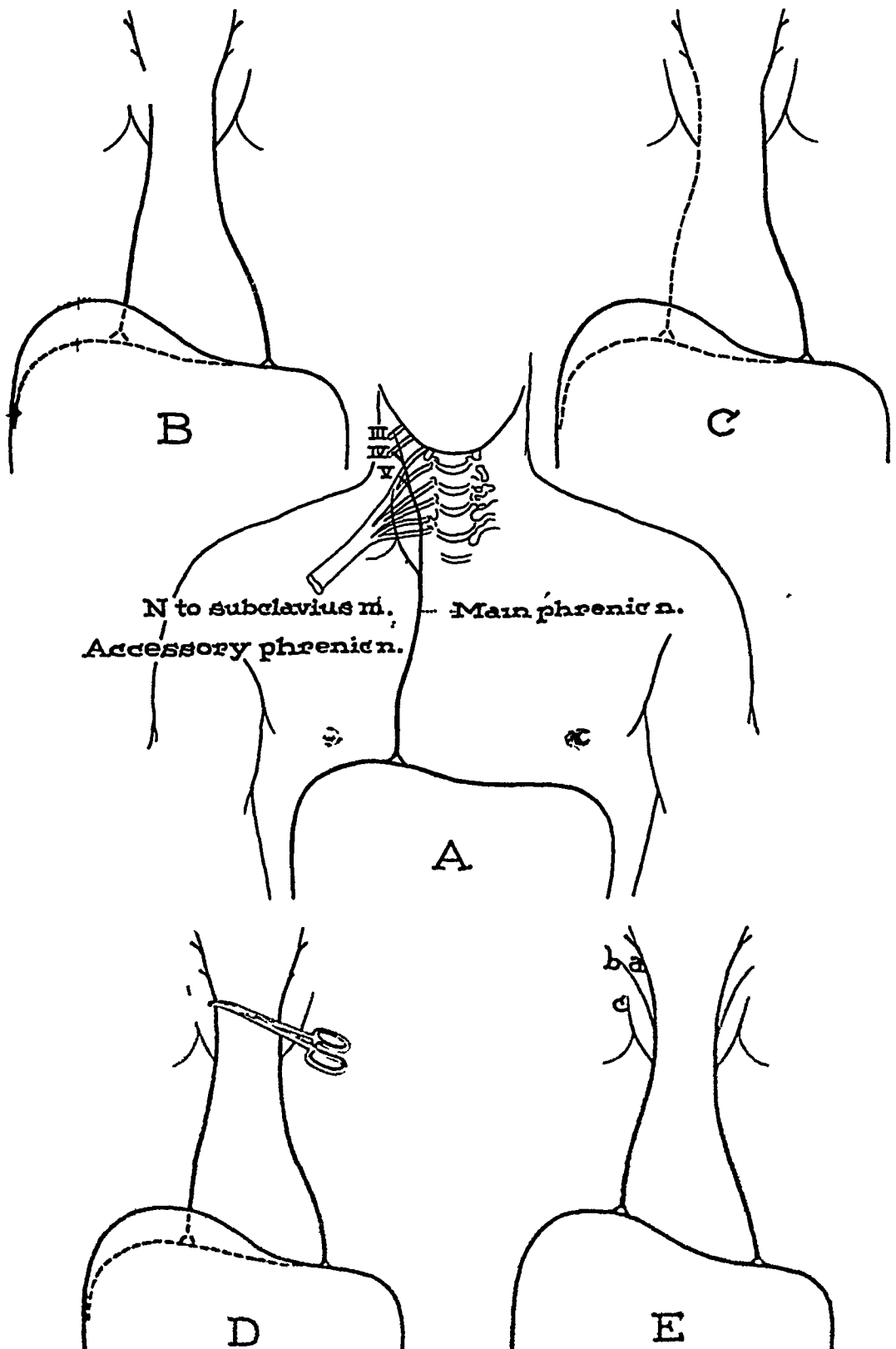


FIG 3 Left film Adhesions of upper lobe to costal wall and of lower lobe to diaphragm, which adhesions are keeping the lung stretched, thereby preventing artificial pneumothorax from closing cavities Right film Rise of diaphragm after phrenicectomy has shortened distance between adherent upper and lower portions of lung, thereby enabling pneumothorax to buckle in the cavities and close them The first thoracic vertebral transverse processes of the two films have been placed on exactly the same horizontal plane so that rise of diaphragm may be seen Though left film was taken two weeks after phrenicectomy the diaphragm had then risen little, six and a half months later it had risen much, owing to its progressive atrophy and stretching Patient referred by Dr John B Barnwell, University of Michigan Hospital





rather frequently does, diaphragmatic paralysis may not be complete. See Fig 4, E, for an additional reason in favor of multiple cervical resection of all phrenic roots. This operation is not much more difficult to perform than evulsion. I have frequently found two or more accessory phrenic roots (one of which, however, may have been the nerve to the subclavius) as well as the main phrenic trunk through a two or two and a half centimeter incision. If no accessory phrenic root can be found I do perform phrenic evulsion if there be no specific contraindications, and personally I have never had any accident occur from evulsion. Anatomical studies show that accessory phrenic roots are present in from 20% to 80% of all persons, I have found one or more nerves in the typical position for accessory phrenic roots in 76.6% of 77 recent consecutive phrenic operations. There is an additional advantage for surgeons to learn to identify all accessory roots as all must be crushed if a temporary phrenic nerve interruption is to be made complete.

It is customary to estimate the amount of pulmonary relaxation following phrenic nerve paralysis by measuring the postoperative rise of the diaphragm in postero-anterior roentgen films. I have recently observed

that a far better conception of the great amount of the lung that the risen paralyzed diaphragm displaces may be obtained from a lateral roentgen film (Fig 6). Incidentally, ascent of the paralyzed diaphragm is not always necessary for a satisfactory clinical result, especially in hemoptysis, although it is usually true that the higher the ascent, the better will be the effect of the operation.

Complete paralysis of a hemidiaphragm causes improvement in more than half of those cases of pulmonary tuberculosis for which it is properly used and, in a few, it seems to be responsible for arrest of the disease. Werner and O'Brien<sup>16</sup> have recently compared the effect of phrenicectomy and of non-surgical treatment upon two groups of one hundred patients each, which groups, however, are not strictly comparable. After phrenicectomy 55.2% of the sixty-seven thin-walled cavities became closed, 38.8% decreased in size, 1.5% remained stationary, and 4.4% became larger. One hundred per cent of twelve cases of moth-eaten cavities closed. After non-surgical treatment only 18.1% of sixty-six thin-walled cavities closed, 12.1% became smaller, and 69.7% became larger. The results of phrenicectomy were not superior in the case of thick-walled cavities, in that none

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by interrupted line) which ruptures connection of accessory phrenic nerve with diaphragm (Felix technique).

D Total but temporary paralysis of right diaphragm by crushing the main phrenic nerve for width of a hemostat's blades, and resection of a portion of the accessory phrenic nerve, whose regeneration is not important for return of diaphragmatic function. Should reoperation later be required to make diaphragmatic paralysis permanent, the accessory nerve would not need to be found.

E Variation in origin of phrenic nerve observed in two patients. Nerve *c* was in typical position for the accessory phrenic nerve and nerve *b* was in typical position for the main phrenic nerve. Nerve *a* lay far medially, back of the carotid sheath, if *b* and *c* but none of *a* had been resected, diaphragmatic paralysis would have been incomplete. Had nerve *b* been evulsed in the belief that it was the only main nerve, it would probably have broken away from *a*, which was heavier than *b* and left *a* intact and functioning. It is likely that this explains the incomplete paralysis that has occasionally been reported to follow evulsion of as many as 10 cm of a nerve that was in the usual position of the main phrenic nerve.

was closed by the operation and 42.8% decreased in size, whereas non-surgical treatment was followed by closure in 5.8% and decrease in size in 50%

In those clinics where phrenic nerve operations are used frequently, complete arrest of the progress of advanced lesions, although it occasionally occurs, is not expected from it and therefore in suitable cases artificial pneumothorax, multiple intercostal neurectomy, extrapleural pneumolysis, or extrapleural thoracoplasty is frequently added as a complementary operation as soon as the maximal beneficial effects of the phrenic operation have been obtained and before the tuberculous disease has spread so far that such procedures cannot be properly considered

Among the operations just mentioned, only intercostal neurectomy will be considered in this paper as its share in this symposium. The procedure may be briefly described by quoting through the courtesy of The Editor of the American Review of Tuberculosis, the summary and conclusions of a recent extensive article on the subject (Alexander<sup>4</sup>)

#### 1 Unilateral multiple intercostal

been startlingly good in three, negative in one in whom lesions in the contralateral lung, intestines and larynx, where they were beyond reach of the operation, continued to progress. Death in one from cardiocirculatory decompensation to which the operation was a final contributing cause, and in the last patient operation three weeks ago has been too recent to permit consideration of the result, although so far the clinical course has been highly satisfactory

3 Phrenicectomy should be performed one or more weeks in advance of intercostal neurectomy

4 Multiple intercostal neurectomy may be painlessly performed in one stage under local anaesthesia. A longitudinal incision is made to the angles of the ribs and two or more centimeters of the second to eleventh intercostal nerves, inclusive, are resected at the costal angles distal to the posterior ramus. Exceptionally for limited lesions, fewer than ten nerves may be resected and, if temporary diaphragmatic and intercostal paralysis be clearly indicated, the nerves may be crushed rather than resected, or they may be injected with alcohol

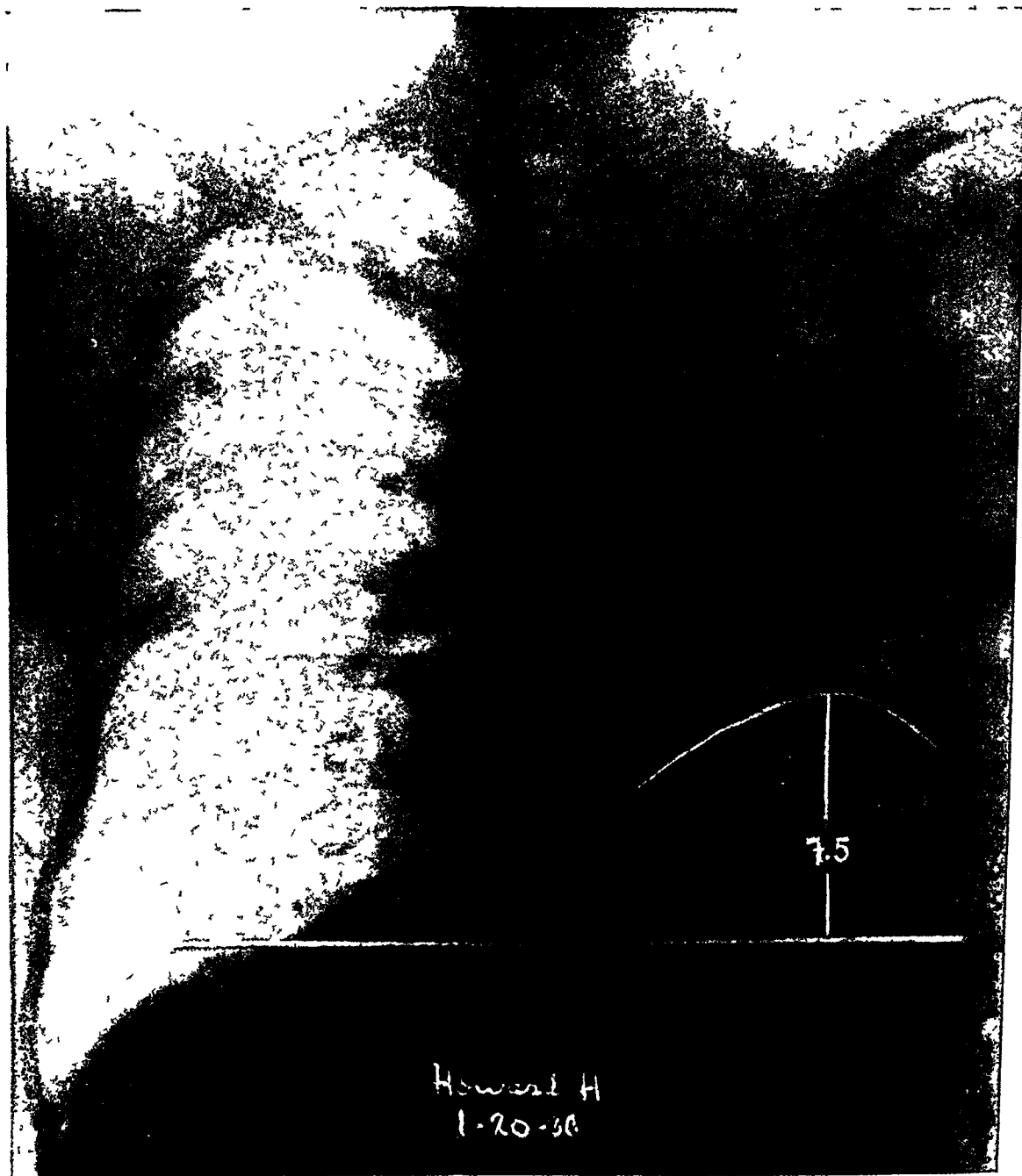


FIG 5 Rise of left diaphragm after phrenicectomy Dome of left diaphragm is outlined with pencil Horizontal line crosses dome of right diaphragm See Fig 6 Patient referred by Dr W E Fawcett, Michigan State Sanatorium

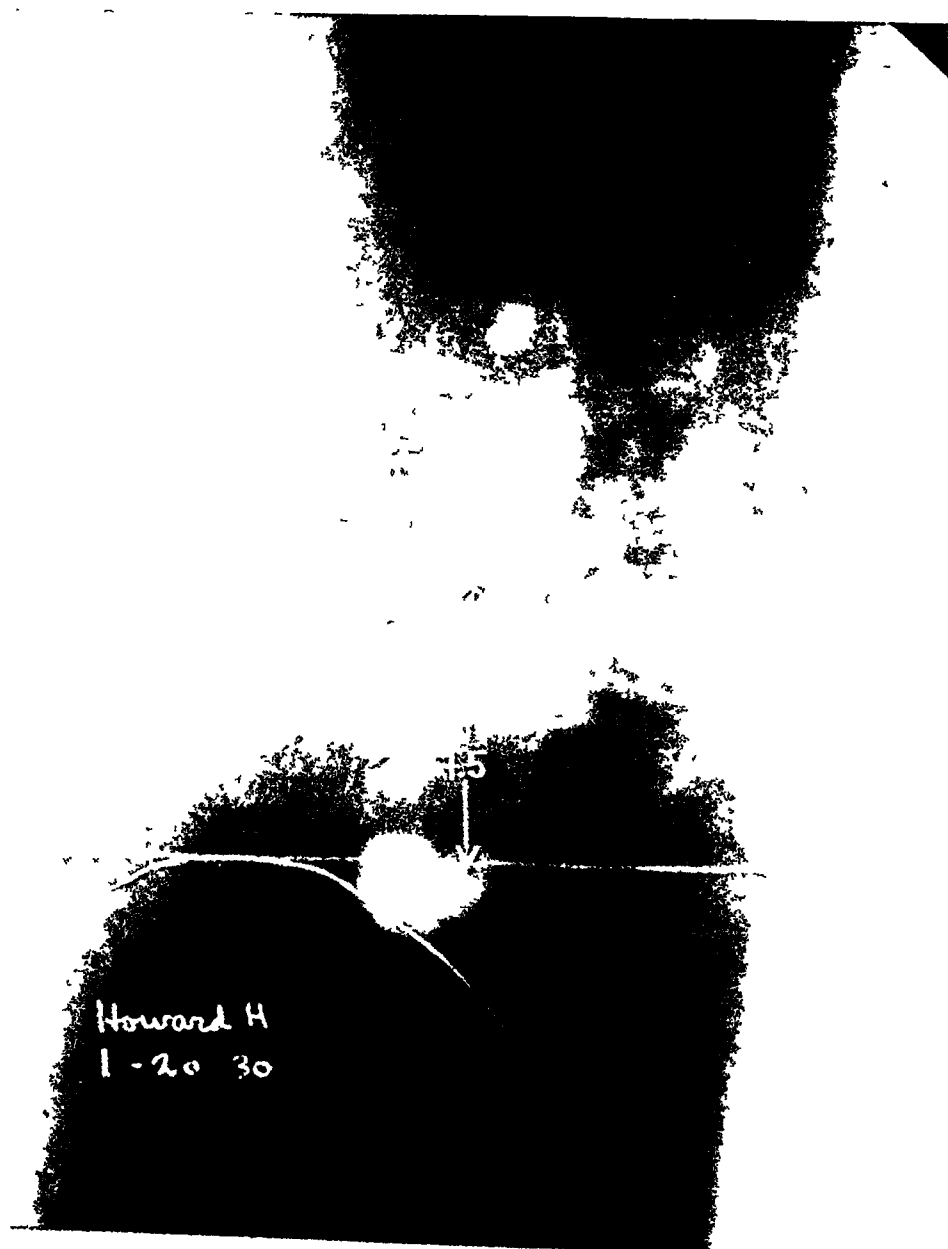


FIG. 6. Same patient as in Fig. 5. Rise of left diaphragm after phrenicectomy in lateral projection. Unparalyzed right diaphragm is outlined with ink. Horizontal line crosses its dome. Risen paralyzed left diaphragm is plainly visible. Only the rise of the left dome above the horizontal line is visible in the antero-posterior projection (Fig. 5) but not the rise and posterior displacement below the horizontal line. The lateral projection therefore, gives a truer conception of the amount of bulge displaced by a paralyzed hemidiaphragm than does the antero-posterior projection.

the patient is in unfit condition for thoracoplasty

9 But I do recommend this operation, with the reservation that my clinical experience with it is based upon only 6 cases, as an apparently effective

substitute for thoracoplasty in those cases in which there is no very large cavity demanding mechanical closure, but in which considerable reduction of respiratory mobility, together with some retraction of the thoracic wall, is desired

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# Thoracoplasty in the Treatment of Pulmonary Tuberculosis\*

By PHILIP KING BROWN, M D , *San Francisco*

**A** CONSIDERATION of the place of thoracoplasty in the treatment of pulmonary tuberculosis presents two main questions. What will this procedure do that cannot be accomplished otherwise, and at what point in the treatment of the disease is this radical procedure indicated. From the background of nine years' observation on about 50 thoracoplasty patients most of them operated upon by Dr. Leo Eloesser of San Francisco, preceded by a thirteen-year period of following the disease in special clinics, tuberculosis classes run after the plan of Dr. Joseph Pratt of Boston in several sanatoria and the tuberculosis wards of a general hospital, it seems reasonable to draw deductions from the results with similar types of patients treated before thoracoplasty and since its use, and to contrast as a control group in the latter class what has happened to the patients for whose relief thoracoplasty was recommended

and when refused. In this country, it has been tried as a last resort on many patients far too advanced to warrant one in drawing deductions as to its value further than that these far advanced cases who survived the operation illustrated how little is the shock in the hands of able surgeons and how much relief of toxic symptoms often follows the closing of cavities. The time should be wholly past when the operation is justified on these grounds alone, for when patients have progressed unfavorably to a critical point, it is unfair to ask a surgeon to do an operation that can only relieve symptoms temporarily. It seems too much like removing the cancerous breast when metastases are already noted. It is frequently the case in any new procedure, that only the desperate and hopeless cases are considered for operation. It is of value to know how advanced a case can stand to operative procedure but it is the part of accumulated wisdom to determine at

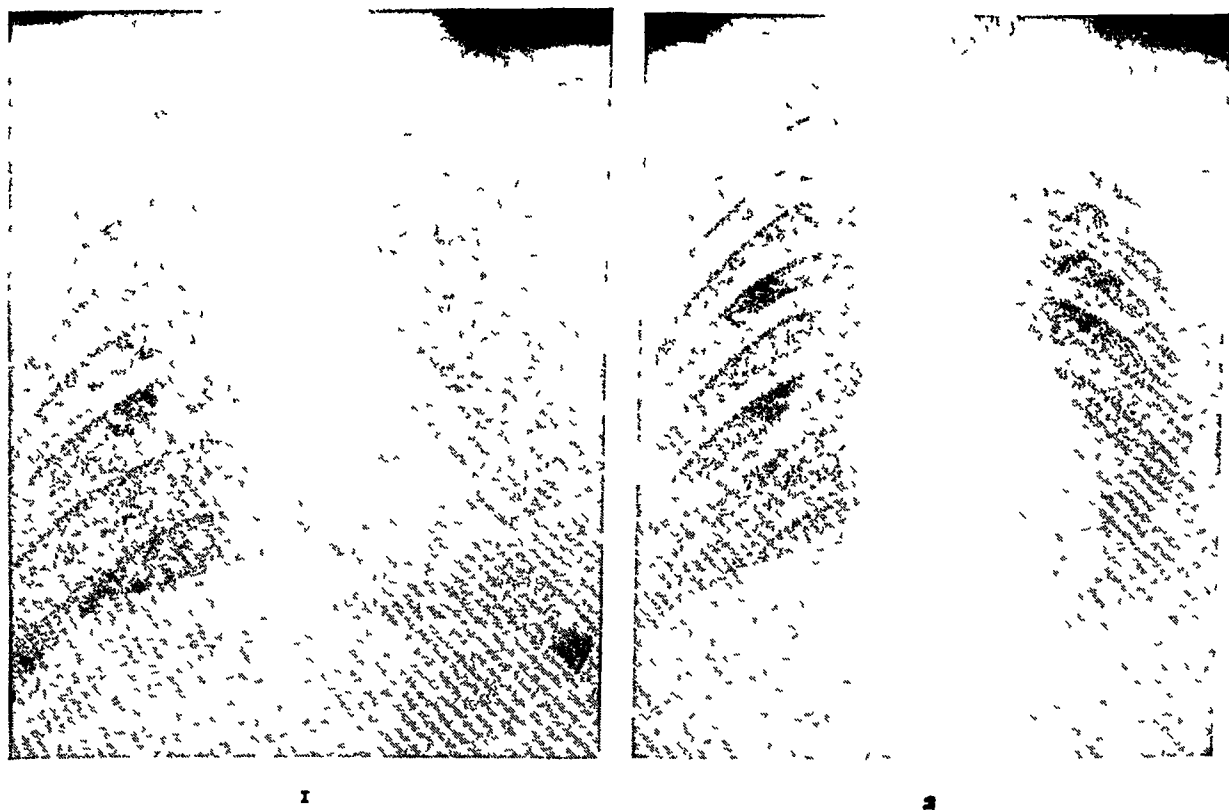


FIG 1—*Cavities bilateral, closing on bed rest alone*  
 1—Bilateral apical cavities size of silver dollar  
 2—Both cavities closed in 11 months rest in bed

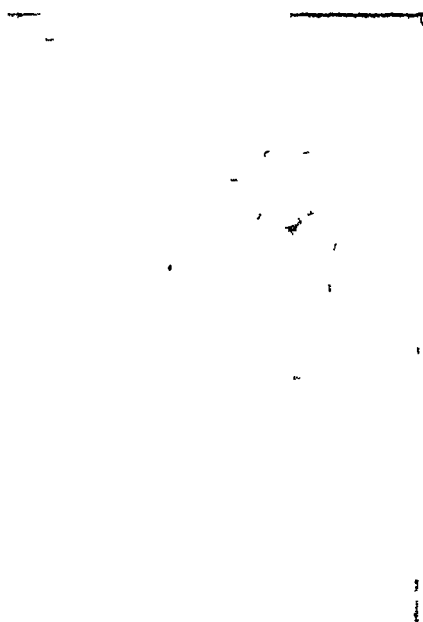
termination of changes resulting from treatment, that he may say with reasonable degree of certainty, the time has come when the patient faces defeat, perhaps several years postponed, without the help of conditions which thoracoplasty alone may bring about

To illustrate this point that there is a right moment for thoracoplasty is the object of this presentation. To show it the more clearly the cases presented are nearly all selected from a sanatorium run for young working women where the visiting staff of three physicians, the director and a surgical consultant have seen and studied every case. The principles of care have been based on supplying to the full the recognized fundamental essentials of sanatorium care, with the introduction of only one variable at a time. A staff evaluation of progress

in all doubtful cases is the rule and each successive step, whether it be postural rest, the use of tuberculin, the elimination of some disturbing physical handicap, the use of pneumothorax or some surgical procedure, has been always the result of conference. Thus 5 people have agreed upon the next factor to be introduced, each time that the patient had reached a standstill. It must be made clear that thoracoplasty is possible only when one side is well enough to carry the full load without danger of breaking down. It has been our repeated experience, as is true also of pneumothorax, that successful thoracoplasty is followed by continued improvement in the arrested process of the other side. The same rule that applies to pneumothorax applies equally to thoracoplasty. The increased burden on the relatively good



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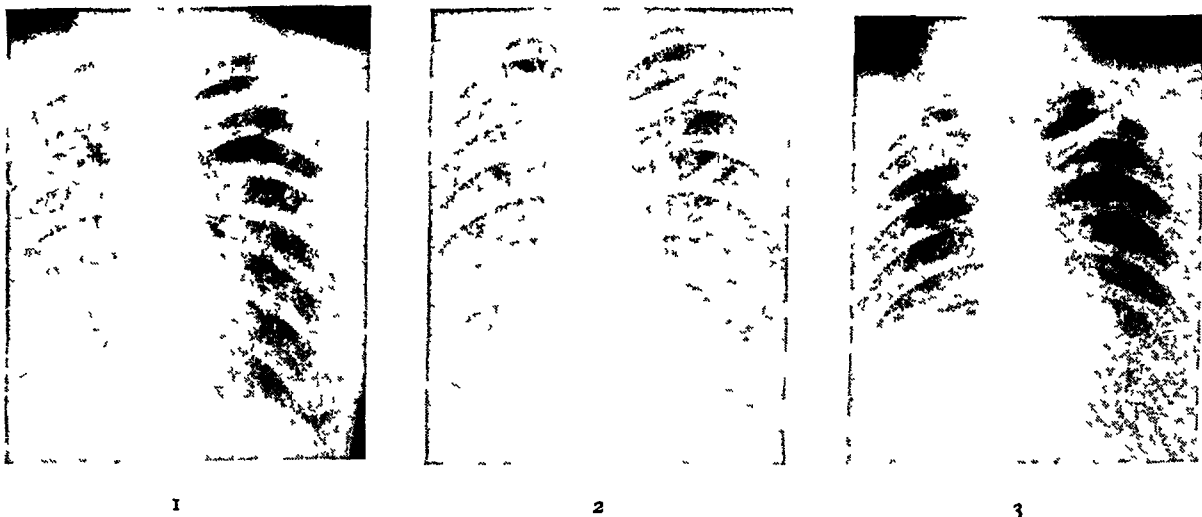


FIG 3—*Phrenicectomy*

- 1—Bilateral process multiple honeycombed cavitations on right, fairly extensive but not intensive process on the left
- 2—After several months in bed coalescence of cavities at right base, small cavity outside left hilus  
Pneumothorax effective only at right top
- 3—Both cavities closed after phrenicectomy

side must not be too great or applied when the lung is not in an arrested condition. A preliminary phrenic nerve evulsion puts only a slightly additional burden on the arrested lung and serves to test its ability to carry an increased load.

Patients who have been for years struggling to close one-sided cavities without success are obviously good cases for thoracoplasty. They have good resistance but are dangerous to themselves and others and must continue indefinitely to lead sheltered lives unless we can close the cavities. Where we find the shoulder low on the affected side, the diaphragm high and the heart, trachea and mediastinum pulled toward the diseased side, and still a cavity persists, thoracoplasty merely continues to its ultimate limit what Nature has struggled often for years to accomplish without success.

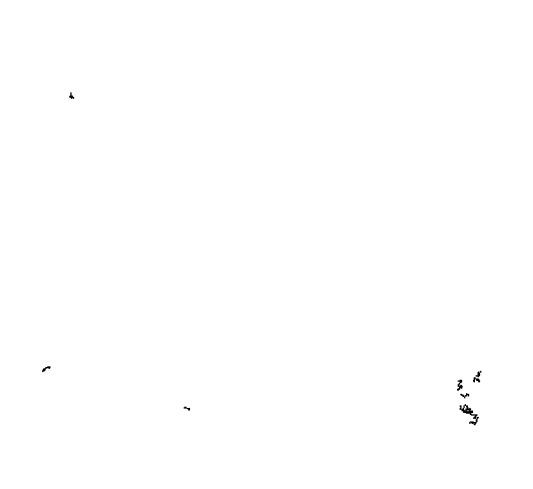
Thirty-six patients (Group I) reached that point and have been operated upon, of whom six are dead of tuberculosis, one of spontaneous pneumothorax followed by empyema where

the operation of thoracoplasty was done in the hopes of relieving a pyopneumothorax and where the patient probably produced the death by overzealous lavage of a fistulous tract, and one of malignant disease after apparent cure of her tuberculosis for 7 years. Nine (Group II) have refused operation, of whom six are dead, one arrested after five years of further sanatorium care and two are still alive after two years, in sanatoria. The average duration of sanatorium or supervised home care of the group who were operated upon was less than one year and in one case only four months. The longest duration of the arrest is the first patient operated upon who previous to thoracoplasty had had seven years of sanatorium care and who has earned her living for eight of the nine years since operation. Two we know have borne children with no disturbing results.

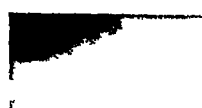
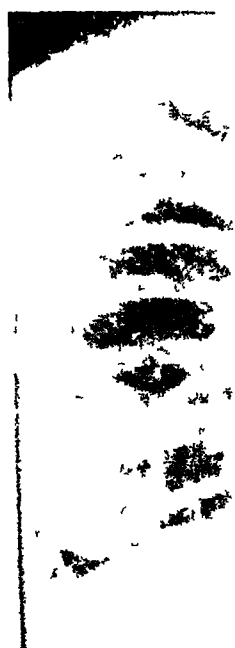
The economic aspect of these patients successfully relieved of activity by thoracoplasty is most gratifying. One has taught school, rides horseback



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and is in every way a normal person. Another is night operator in a hospital where she has continued to gain for many months. Many of them resumed normal home relations as housewives for the first time in periods varying from 3 to 10 years. One is a Public Health nurse on full time work still after 6 years of steady work.

Not the least advantage of the time-saving aspect of thoracoplasty is the overcoming of an almost hopeless demoralization that long years of sanatorium life is too apt to induce. It seems fair to raise the question also as to whether it be not vastly preferable to undergo thoracoplasty rather than submit for 9 years, as did one of our patients, to refills of a pneumothorax. So satisfactory have been the results in well chosen chronic cavity cases that it should appeal to anyone as the method of choice if for sufficient reason it seemed desirable to keep a lung compressed permanently. I doubt if the general run of patients upon whom pneumothorax has been done have averaged as well as have these girls who have been compressed surgically.

There can be no question but that thoracoplasty should be resorted to at once, if it were justifiable to consider it at all, provided repeated attempts at pneumothorax should be unsuccessful in bringing about satisfactory compression. Our experience as shown by Group III argues against too long delay. This experience has been called attention to very pointedly by Brauer, who learned to do his own surgery, and by the Matsons in our country, who have contributed most important-

ly to this subject of the necessity of taking advantage of every factor in a case in determining the opportune moment for any radical method of interference. Recognizing this, we have invited surgical consideration of many patients whose progress was not satisfactory, long before we were ready to ask for operative relief. It seemed unfair to invite a surgeon to operate upon a patient unless he had become familiar with the progress of the patient up to the point where his aid seemed immediately necessary.

There were no operative deaths in this group. The deaths from progress of the tuberculosis were due in one case to the huge size of the cavity, in another to the fact that there were three cavities vertically placed and not enough resection was accomplished to close them, although several resections were done and even the clavicle was shortened. A further group should be referred to in order that the picture may be complete—patients known to be hopeless because of long continued care with improvement on one side and progress of the disease on the other. These patients had been accepted by the sanatorium because of our study of the possibilities of surgical relief with the distinct understanding presented to them or their families in writing and agreed to, that if sufficient improvement took place in the less advanced side to warrant an attempt to compress the relatively bad side, this should be tried by progressive means until accomplished. In this way there was no question of persuading the patients and they lent themselves unusually well to each ef-



FIG 5—*Thoracoplasty refused*  
1—Large right apex cavity, infiltration moderate in rest of right side  
2—After unsuccessful efforts to compress by artificial pneumothorax for 4 months  
Died within 1 year



foit of ours to help Two developed colds contracted in a closed machine from the husband of one while enroute to the hospital for preliminary phrenicectomy Both had rapid lighting up of their trouble and both died Seven had relapses at the sanatorium and died, five of them before all the staff and the surgeon could agree that the time for the final step had come, and two because of their own procrastination It seemed to me fair to include all of these in the contrast group Still another group should be mentioned in contrast to this last most discouraging one, and that is the six patients admitted for surgical consideration who improved on both sides, or if unilateral at the start, they improved on the affected side so steadily and so rapidly that they went on to arrest without the help of even pneumothorax Several had had this procedure tried without success before coming to us Plates are made every two months of all patients considered for surgery, the same technique being used so that cavity measurements are accurate Fever records, measured sputum, weight gain, heart action and all the possible variables that enter into the estimation of progress are considered every two months by the staff in each of these cases One of these patients upon whom pneumothorax had been unsuccessful on account of adhesive pleurisy was summoned home to care for a father after the mother had died, and in the emergency, the right mid lobe cavity having remained stationary too long, a phrenicectomy was done which fortunately closed the cavity Two years have gone by and the disease is apparently arrested

The case is referred to because it is not always possible for the mediastinum to shift or the rib cage to be contracted by adhesive pleuritis, and cavities remain unchanged in size even after months of postural rest

It is plain to the specialist in tuberculosis and to those general practitioners like the writer who have a deep interest in making tuberculosis a treatable disease and not a boarding house or custodial job as it is too often, that upon first examination of a patient with well established pulmonary tuberculosis, every collectable bit of dependable evidence must be assembled and this includes a carefully taken detailed history of every incident bearing in any way on the patient's condition—old temperature records—x-ray plates, weight records, pain, coughing period—all this helps to evaluate the patient's chances and enables the examiner to lay out, in his own mind, at least, a plan of action.

At this point it is interesting to note Bachmeister's statistics of the experience of Swiss Sanatoria with cavity cases "Given a cavity the size of a cherry at the onset of sanatorium care and unless that cavity has steadily shown a tendency to close and does close or has been closed by artificial means, only 20 per cent of chances exist that the patient is alive in six years even with continuous sanatorium care" This emphasizes what our own experience has taught us in its small way, that the careful physician makes his preparation for a siege when he assumes the defense of a patient with well established pulmonary tuberculosis and at all times he must conduct





FIG 8—*Apicolysis*

1—Two large cavities at left top under sternum

thorax impossible

2—Apicolysis—top 6 ribs

Well and working within 1 year

Under sanatorium regime 7 to 8 years Pneumo-

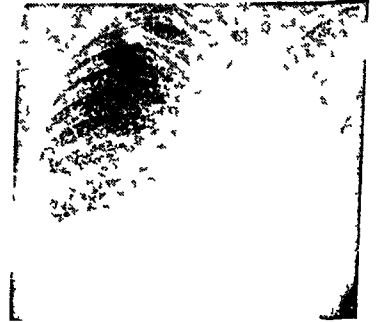
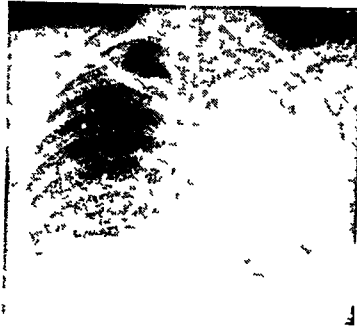
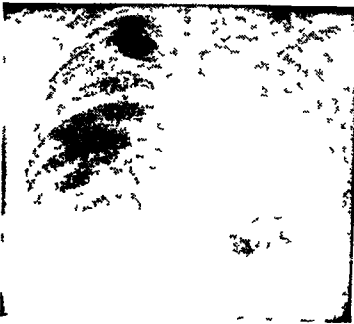


FIG 9—*Thoracoplasty*

1—Extensive cavitation of the left top Pleuritis Retraction to left of mediastinum and heart

Diffuse but slight process in right upper

2—Right upper completely arrested after 4 months

3—Thoracoplasty with complete cure Patient has borne children Well for 6 years

the case so that the patient's increasing or diminishing chances are evaluated properly so that the pursuit of one method of help may not be continued too long to the jeopardy of the next and the next moves in the game. In other words we must remember Pryor's dictum, never truer than now, that "We must treat the consumptive in the right way at the right place at the right time until he is cured and not

in the wrong way at the wrong place and at the wrong time until he is dead"

#### GROUP I

36 thoracoplasties in 9 years, because of the failure of rest and pneumothorax to close large cavities

6 died of tuberculosis,

1 died of cancer after 9 years of health,

1 died of sepsis, 2 years following a thoracoplasty for pyo-pneumothorax

8 died

## GROUP II

9 offered thoracoplasty after failure of other methods and operation refused Of whom

6 are dead,

1 clinically well,

2 in sanatoria after 2 and 3 years further care

## GROUP III

9 far advanced cavity cases admitted for pneumothorax or thoracoplasty or both and died in relapses after decided improvement Death attributed primarily to delay in operation

## GROUP IV

6 far advanced cavity cases admitted for pneumothorax or thoracoplasty or both if found necessary and recovered without either procedure

Several of these had bilateral cavities of size in excess of 3 cm diameter

## SUMMARY AND CONCLUSIONS

1 While it is true that large cavities may close entirely as a result of postural rest, pneumothorax, phenicectomy or intrapleural pneumolysis (Jacobeus), one should not postpone too long a trial of thoracoplasty in cases that come to a standstill *before* the closure of large cavities, or that have constantly recurring hemorrhages in spite of what compression can be effected by pneumothorax

2 The deformity from complete unilateral thoracoplasty is neither an esthetic nor economic handicap The objection offered to thoracoplasty because of its deformity is best answered by Dr John Alexander who writes (National Tuberculosis Association, Vol. XXV, Page 96) "The so-called deformity following thoracoplasty should not be properly included in a basic discussion of the relative merits of the two operations (multiple intercostal neurectomy) Ordinarily the deformity following a properly executed thoracoplasty is so little that the term is a misnomer unless intended in its literal and not its usual sense"

3 It must not be recognized as a cure, but as a means to cure where physical conditions prevent the closure of cavities

4 Thoracoplasty is an aid to Nature's method in closing cavities where its success is threatened by seemingly insurmountable difficulties, size of cavity, its being held open by extensive adhesions, the recurrence of large hemorrhages and the failure of lesser efforts to help



# General Considerations of the Rôle of Surgery in Pulmonary Tuberculosis\*

By DR GERALD B WEBB, *Colorado Springs, Colorado*

**T**UBERCULOSIS in any part of the body is generally considered to be a medical disease. Surgical intervention then is a confession of failure on the part of the physician. At present tuberculosis of a single kidney is the only condition that physicians instantly submit to operation. Chisholm's complete cauterization operation for rectal fistula is doubtless a surgical success. So-called surgical tuberculosis is, strictly speaking, not surgical. Tuberculous joints are treated by rest, by splinting and by sun therapy. For the most part tuberculous lymph nodes, tuberculous testicles, and tuberculous intestines, are not operated, a tuberculous larynx is treated by a régime of silence and by heliotherapy, and tubercle of the retina or choroid is one type of disease which certainly is benefited by tuberculin therapy. The surgical procedures advocated in pulmonary tuberculosis are all methods of increasing rest of the lung, and rest is the only successful treatment yet devised for this disease. The symposium covering surgical procedures for obtaining increased rest of

the tuberculous lung has been splendidly presented. There are two good reasons why the development of such surgical assistance has come to pass. Firstly, the diagnosis of pulmonary tuberculosis is lamentably late, and secondly, the régime of rest in sanatoria and elsewhere is rarely efficiently carried out. The early diagnosis of pulmonary tuberculosis would be more frequently made if all patients were submitted to x-ray study, and if all children entering and leaving High School were given the advantage of this comparatively inexpensive examination. The correct régime of rest is costly, and sanatoria cannot always afford the nursing care which is so necessary. Surgeons who take charge of tuberculous joints do not allow motion of these joints for a very protracted period, but physicians have never yet realized the prolonged and complete rest that is necessary for the recovery of their patients with pulmonary tuberculosis. The prosperous classes can obtain the thorough rest, the poorer cannot. Then temperaments must be considered, for as Solly wrote "The wise have four times as good chance to recover as the foolish." In this regard Shakespeare's words are pertinent.

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\*Presented before the American College of Physicians February 14, 1930, Minneapolis, as Part of a Symposium on 'The Surgery of Pulmonary Tuberculosis.'

"And all our yesterdays have lighted  
fools

The way to dusty death"

And again —

"How poor are they that have no  
patience!"

What wound did ever heal but by  
degrees?"

Decision to submit a patient to surgery will depend in part on the ability of the patient to finance a longer period of rest to a certain degree on the mentality of the patient and also to the degree of the disease. Under my care at present is a patient who, two years ago, was advised by his physician to go to Sauerbrück for thoracoplasty. The patient under rigid rest régime has done remarkably well and his sputum is free from tubercle bacilli. It is not understood by the profession that tuberculous pleurisy, especially with effusion, is a serious infection which needs several years' watchful after-care. Such patients, who are apt to develop serious pulmonary tuberculosis, supply a not inconsiderable number of subjects for surgical aid.

I cannot agree with a recent writer that "practically every demonstrable unilateral tuberculous lesion should have some form of (surgical) compression therapy and that almost none of them should be left to bed rest alone." However, compression therapy must be considered earlier in those patients who for one reason or another cannot carry out the proper prolonged rest régime. Three years ago before this association I advocated and described postural rest for unilateral lesions, and the application of shot bags

for bilateral lesions. After sixteen years, practicing these principles, I still believe that this method of treatment should be first tried and faithfully carried out for at least six months to a year. Roentgen studies from time to time will indicate the progress that is made apart from the clinical benefits.

Within the last week a lady from Michigan dropped in to pay me a social call, who sixteen years ago had been directed to me for pneumothorax treatment but who completely recovered under postural rest.

Artificial pneumothorax is our second choice, but in only one-third of the patients in which this is attempted is the result apt to be satisfactory. It has dangers which have been mentioned. Septic pleuritis is reported by some authorities in 5% of the successfully treated, severe pleuritis in 30% and purulent pleuritis in 4% to 11%. The last may vanish under skilled treatment, or may lead to amyloid disease if thoracoplasty cannot be performed. The chief objection to pneumothorax is that it must be kept up for at least three years and preferably for a longer time. It is, however, a procedure which may be discontinued and can result in recovery and full expansion of the diseased lung. Artificial pneumothorax is perhaps the simplest of the surgical compression methods and can be applied safely to advanced cases even to those with laryngeal and intestinal complications. Improvement in the contralateral lung has been noted by Peters, Loomis Sanatorium, in 7%, and progress of disease or exacerbation in this lung in 25% of the cases receiving successful

pneumothorax. Similar figures probably represent the results in the contralateral lung following thoracoplasty.

The same author reported 42% living after two to fourteen years and 24% of these were in satisfactory condition. Matson, reporting 1,004 pneumothorax patients, found 32% clinically well and 32% dead. In general, results from artificial pneumothorax are claimed to be twice as good as without this treatment. The Jacobaeus method of intra-pleural pneumolysis, improved and cleverly performed by Matson, has led to a slight increase in the successful results of pneumothorax. This technic applies chiefly to the string like adhesions. Kinsella believes the band type of adhesions are best studied by thoracotomy. If such adhesions cannot be severed, the hand can be inserted to squeeze down a cavity. Pneumothorax has saved many lives when administered to patients with pulmonary hemorrhage which could not be otherwise controlled. It has proved, too, an excellent remedy in tuberculous pneumonia. In patients with pleuritic effusion, which requires removal, sterile air should be introduced to replace the exudate.

Phrenicectomy is of more recent date, first advocated by Styertz in 1911, and it is perhaps too early to fully evaluate this procedure. Like thoracoplasty when once done it cannot be undone. Brilliant results have been seen including the healing of apical and basal disease. There have also been numerous disappointments and cavities have been noted to increase in size. Following this operation certain complaints of distressing dyspeptic symptoms have been

made, more frequent in left-sided cases. These may, however, be only temporary. Truesdale has well demonstrated, in moving pictures, the peculiar undulating motion of the diaphragms in dogs, after section of one phrenic. He has also pointed out the possibility of some displacement resulting at the lower end of the esophagus. Some patients have complained of a temporary difficulty in swallowing following this operation. Phrenicectomy is to be considered in patients, who, because of adhesions, cannot receive artificial pneumothorax. It is of value following pneumothorax to help in the absorption of pleural fluid and to reduce the thoracic cavity when re-expansion is allowed. It is also of value for pulmonary hemorrhage. Used as a preliminary to thoracoplasty, the extraction or crushing of the phrenic nerve has made this procedure more complete, and at times has saved the patient from the more severe operation.

Thoracoplasty is an operation limited to a small number of well selected cases. In the past there were few surgeons sufficiently skilled to undertake this operation. The mortality rates reported in the first two months following extrapleural thoracoplasty have been as high as 13%. The patients selected are those with little or no disease in the contralateral lung, those in whom pleuritic adhesions have prevented successful pneumothorax, those in whom large cavities or cavities near the surface would render the latter procedure dangerous, and those with a marked cirrhotic type of disease. The operation should be done in two or more stages, and some surgeons

advise operating first over the area diseased. If the upper lobe is diseased then the upper ribs are removed first, and vice versa. Alexander's statistical studies show cure resulting in over 36% of patients operated. Partial and lateral thoracoplasty have at times yielded excellent results. I cannot agree with those who would supplant all pneumothorax treatment by thoracoplasty. Theaile believes that thoracoplasty influences the disease more promptly and permanently and the patient is spared the long medical supervision demanded by pneumothorax treatment. In bilateral disease a combination of the several surgical procedures has at times been successful. Bilateral pneumothorax has been simultaneously induced. Our own results have been more favorable when pneumothorax has been given upon one side before started on the other. In some cases pneumothorax has been carried out on one side and phrenicectomy or thoracoplasty on the other. The degree of disease, the constitution of the patient, the skill of the individual surgeon, and the type of after care, are factors which make statistical deductions difficult and fallible. These factors are applicable to all methods of treatment. Some physicians will procure better end results by the rest treatment than others. With many, the complications of pneumothorax will not be as high as those reported above.

A tendency has been noted for some physicians well trained in tuberculosis to develop into thoracic surgeons.

Such men better appreciate what patients can endure and understand the necessary after care.

In my experience, surgery in pulmonary tuberculosis does not markedly shorten the period of time that patients need most careful medical care. Whatever operative procedure is followed patients must have from three to five years of skilled medical observation.

It is to be hoped that surgery will aid still more in reducing the death rate from tuberculosis. Some 50% of patients discharged from sanatoria die within five years following their dismissal. It will be natural for patients to request surgical procedures which give promise of more rapid cure. Are we in a transition period leading to substitution of surgical methods for other rest measures? I think not. It must always be remembered that tuberculosis tends to relapse and that whatever method we adopt to secure rest of a diseased lung, the permanent cure cannot be greatly accelerated and several years are necessary to build up what is generally termed "resistance."

That so many excellent results have been obtained in patients who were poor surgical risks is a forecast that many patients in the future will receive compression therapy earlier than in the past. But the decisions to submit patients to surgical procedures must remain with the competent physician who knows tuberculosis and whose experience must dictate the measures to be followed.

# The Limitations of Heliotherapy in Pulmonary Tuberculosis\*

By BERNARD LANGDON WYATT, *Tucson, Arizona*

IN this discussion of heliotherapy in pulmonary tuberculosis from the standpoint of its limitations, it must be emphasized at the beginning that reference is made primarily to personal experiences under meteorologic conditions that prevail in Southern Arizona. No attempts at "generalizations" will be made for a number of obvious reasons, among which only one will be noted, i.e., that qualitatively and quantitatively these solar radiations are not identical with those at other latitudes and altitudes, not to mention the meteorologic variables peculiar to the desert.

Not only will all generalizations be omitted, but also, there will be no discussion of the comparative effectiveness, (from the standpoint of biologic reactions), of radiations from the sun and artificial sources of radiant energy.

The term heliotherapy will be used to describe the exposure of the surface of the body to the *direct* rays of the sun, although it is clear that such exposures necessarily involve indirect radiations from sky reflection as well as the influences of air currents. This question of indirect radiations and

aerotherapy is of more than passing interest and there are some indications that the limitations of *direct heliotherapy*, which will shortly be considered, do not pertain to the same extent and degree to aerotherapy and the effects of indirect radiations from sky reflection.

The difference and distinction between *climatic rest-cure* and *direct solar radiations* are obvious, even though the difficulties to evaluating their separate effects are always great. These difficulties, together with the fact that pulmonary tuberculosis is a disease with a tendency to "self-healing" in many cases, are probably responsible, to a certain extent at the least, for the difference of opinion as to the *actual results* of heliotherapy in pulmonary tuberculosis that is reflected in the medical literature of this and other countries.

Some twelve years ago Rollier stimulated my interest in the possibility of using direct solar radiations as an important adjuvant to other measures in the treatment of pulmonary tuberculosis. In his experience, the patients treated by heliotherapy were those with the "surgical" forms of tuberculosis, whose clinical manifestations of the pulmonary form were of secondary importance and of the usual mild type with a tendency to rapidly become

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\*Presented at the Fourteenth Annual Clinical Session of the American College of Physicians, February 14, 1930, Minneapolis, Minn.

quiescent Nevertheless, Rollier's views about the value of heliotherapy were those expressed later in the 1923 Oxford edition of his book in which he states

"This book would be incomplete if so important a subject as pulmonary tuberculosis were to be ignored, to treat it adequately is beyond our power as our experience has been almost entirely confined to the surgical manifestations of the disease We have, of course, had occasion to treat large numbers of patients who presented active pulmonary as well as surgical lesions (about twenty per cent of all cases), but hesitate to draw conclusions from them as they can hardly be considered as typical cases of pulmonary tuberculosis It has been

stated that heliotherapy is liable to produce haemoptysis and foci of congestion in the lung, although perfectly true that these results may be produced by prolonged exposure to sunlight, especially in hot, thundery weather, such accidents are easily avoidable if proper attention be given to technic We have frequently found that with patients subject to hemoptysis a carefully controlled course of sun baths, far from increasing this tendency, caused it to disappear

Properly applied, I am convinced that heliotherapy would be a useful factor in the treatment of the great majority of cases of pulmonary tuberculosis "

We have here a declaration which has undoubtedly influenced many clinicians in the United States as well as in Europe There are, as a matter of fact, numerous reports substantiating Rollier's opinion, but when these data

are subjected to careful analysis they are frequently not entirely convincing

During the past five years it has been my privilege to devote a great deal of time to the study of the results of direct heliotherapy in pulmonary tuberculosis under conditions permitting of the most careful control of dosage and methods of exposure Almost every type and stage of the disease—with the exception of acute or rapidly progressive cases—have been represented and the results have been analyzed in a careful and critical manner The work was started with the sole idea of finding out the facts and not to prove or disprove any pet theory The progress of patients who did not receive direct solar radiations was studied for comparative purposes

Patients with the so-called "surgical" forms of tuberculosis who also had clinical manifestations of pulmonary tuberculosis were excluded for the reason that in cases of extra-pulmonary involvement the lesion in the lung is usually of a mild type with a tendency to become quiescent rapidly

In the original report on these observations, which appeared in Hospital Progress early in 1928, about three hundred cases of pulmonary tuberculosis were included Subsequent analysis of these records, however, has resulted in the exclusion of one hundred cases in order that comparisons between the results of direct heliotherapy and climatic rest-cure might be made with greater accuracy

It is clear that the series is too small for definite conclusions to be arrived at, but it is a matter of considerable interest that *the number of patients showing appreciable improvement that*

*might be attributed solely to direct heliotherapy was negligible*

It was clearly demonstrated that, when carefully supervised, general irradiations do not tend to produce hemoptysis, but it was necessary to be constantly on the alert to keep the exposures below the point of stirring up focal reactions

There were some indications that a few patients with chronic fibrosis might be benefited by indirect radiations from sky reflection, but it was obvious that direct heliotherapy had definite dangers unless properly supervised

It was furthermore found that the mathematical precision with which attempts were made to measure dosage was impracticable, as well as unnecessary, and that a considerable variation in the amount of solar radiations was tolerated without any clinical manifestations whatsoever

The results derived from direct heliotherapy in pleural tuberculosis were most gratifying, and this was also true of tracheo-bronchial lymphnode disease. Furthermore, it appeared that exposures to the direct rays of the sun were of great value in preventing the development of intrapulmonary lesions in cases of hilum tuberculosis and primary pleural involvement

Sunlight, which was formerly used extensively in Switzerland for the treatment of pulmonary tuberculosis,

has been given up almost completely and Jacquerod, after many years experience with several thousand patients, has discarded it entirely.

In a personal communication recently received from Mayer of Saianac Lake, he writes, "As to the use of direct sunlight in pulmonary tuberculosis, I think that most of the reports have not been on controlled cases, and, therefore, biased in its favor. We have given it a very fair trial here in the summer time, and only in the rarest instances was I convinced that it helped—just about the same as in the isolated case that responds to tuberculin. On the other hand, I have seen other exposures in these cases do real harm. The way I feel about it is this—when I think of extra-pulmonary tuberculosis I immediately think of light. On the other hand, when I think of pulmonary tuberculosis, I do not think of light

We have constructed a pure quartz solarium at our new National Vaudeville Artists Sanatorium. I will, there, very thoroughly study with two physicists in our laboratory what these minimal doses of light will do in the wintertime in a thoroughly heated quartz solarium, to pulmonary tuberculosis, but I anticipate that rarely ever will the sunlight turn the tide in favor of the patient in a case of pulmonary tuberculosis that has otherwise been considered as an unfavorable case."

ber of examinations for a sufficiently long period of time

In the consideration of tuberculosis, study of certain reactions of the blood serum are frequently of definite value. This is so in four classes of patients and of relative value in the order named

Firstly — those whose clinical picture resembles that of tuberculosis, frequently called 'Tb Suspects'

Secondly — those who have been recently exposed to massive infection by the *Bacillus tuberculosis*, commonly known as 'Tb Contacts'

Thirdly — definitely tuberculous patients in the stage of activity

Fourthly — definitely tuberculous patients arrested or apparently cured

The two serological reactions I refer to, are the 'Tuberculo-Complement Fixation' and Caulfeild's Inhibitive. My comments are based on — observations before the war at Muskoka Hospital, since the war at the Dept. of Pensions and National Health Chest Clinic with an annual attendance of 6000, my own clinic at the Western Hospital with an annual attendance of 2000 and my own patients, the latter supply most of the examples to be given today. The total number of tests in our group of five clinicians is 25,000<sup>1 2 3</sup>

Before proceeding to discuss the practical interpretation of serological reactions in actual cases, several qualifications or limitations must be stated. The *technique* of the inhibitive appears to be more difficult than that of the Wasserman and I must remind you that many internists will not accept a single Wasserman report unless it coincides with their clinical conception of the particular case. They send a sec-

ond specimen to another laboratory (I recall several of my own mistakes in the interpretation of the Wasserman reaction)

Four years ago Perla of Philadelphia attacked the validity of these reactions as serological tests and consequently felt our clinical interpretation was not correct<sup>4</sup>. On the contrary Dr. Norwich of Toronto in the January number *Amer. Rev. of Tuberculosis* confirms the original observations on the specificity and reliability of the tests<sup>5</sup>

It seems to have been forgotten that the late Dr. Ray Hodge succeeded in carrying out this inhibitive test independently of Caulfeild. Also the last article on the technique from the Connaught Laboratories was by Hodge and MacLennan<sup>6</sup>

The *interpretation* of both Inhibitive and Fixation reactions also presents difficulties. This is caused by the frequently varied successive reactions in the same positive case of Tuberculosis. *If one accepts* that the variations in the Inhibitive reaction are indicative of varying immunity in the tuberculous patient the difficulty is minimized. When Caulfeild evolved the Inhibitive he first regarded it as indicative of immunity<sup>7 8</sup>

It follows, therefore, that for definite aid in the study of a case, *a series* of serological tests *may be* necessary, rather than one or two, and is to be looked upon as the only way of properly employing the tests. It is exactly in this particular point that we find fault with the critics of these tests, that they have been content to judge on a single reaction.

The tests, therefore, are of *primary* value and easier interpretation for diag-



nosis, in clinics or institutions dealing with suspects and contacts. They are of *secondary* value and more difficult interpretation, in prognosis, in Sanatoria or to Clinicians having to decide upon the future course of an arrested case, or upon whether radical measures such as pneumothorax or thoracoplasty are advisable.

The Dept. of Pensions and National Health Chest Clinic then has use for the reactions in three classes out of the four—in all classes excepts Contacts.<sup>9</sup> The *Civilian Chest Clinic* can use the tests in all four cases.

The possible value to Insurance Companies should also be considered. A man is refused insurance by most companies until one year has elapsed after his wife's death from tuberculosis. According to our observations, this is the very time when the disease (tuberculosis) should be looked for in the contact. In several hundred closely watched adults we have not yet found demonstrable tuberculosis under 15 months after exposure. The incubation period in our series we would say varies from one to five or seven years.

As to their value in surgical tuberculosis, Dr. Horace Macintyre's paper read before the Ontario Laennec Society in 1926 showed 95% positive reactions in definite tuberculosis.

The inhibitive and T C F are totally different. In many cases we do not expect to get a positive *inhibitive*. It is also regrettable that there are examples of tuberculosis in which the *fixation* does not occur.

We obtain, as you will see in my examples, totally different serological graphs in different clinical pictures, and we think they coincide.

In no post-mortem examination at Christie Hospital have we been shown to be wrong in our written opinion.

In our anxiety to arrive at the most accurate interpretation of these reactions, it may be worth while giving some of the ten points outlined by myself in 1924 at Ottawa, noting at the same time what modifications, if any, we might make five years later.<sup>10</sup> I will throw these on the lantern screen that they may be more carefully studied.

After these are shown I shall display also on the screen, x-ray pictures of pulmonary cases and their graphic serological charts, to give examples of (the two) the classes of patients in which serology most frequently assists.

Please note, as my confrère, Dr. Caulfield has said, that we place serology alongside of other forms of examination as just another aid. Would we rely on that recent and valuable method of examination—the X-ray Stereoscopic Picture, to the exclusion of history taking or physical examination? The Roentgenologists would agree with our answer, 'Certainly not.' Neither would we be *without* the X-ray. Just so, serology in our experience has its own definite place of value.

<sup>11</sup>Allowing that certain reaction combinations must be interpreted differently in different clinical pictures, I would say that we regard the combined inhibitive and tuberculo-complement fixation as specific reactions and as helpful in the diagnosis and prognosis of tuberculosis.

In all cases of suspected tuberculosis, I draw blood for these tests and would here state some particular points to be noted in the interpretation, to-

gether with the chief limitations in their use

As you may know, the results of the inhibitive test are reported from the laboratory in the phraseology of "First," "Second," or "Third" class or more rarely "Negative" Inhibitive. The fixation is reported in units of complement fixed, the fixation of 2,  $2\frac{1}{2}$ , or 3 units being regarded as positive

Point 1 Any or all of these may occur in the tuberculous, but only third-class and negative inhibitives occur in the normal, and the third-class is always found in the normal adult. When the apparently normal adult gives any reaction varying from third-class, we are open to suspicion of tuberculosis.

Point 2 If the result is second or first-class inhibitive I take it as strong support to a suspicion of tuberculosis and believe that biological tubercle exists. If clinical symptoms or signs obtain simulating tuberculosis, I assume the presence also of clinical disease. It may be present to ever so slight an extent and may not be otherwise demonstrable.

Point 3. A third-class inhibitive with negative fixation, lends support to the exclusion of tuberculosis but a single negative has little influence on my opinion, if I have already made a probable diagnosis of tubercle. As in other tests, a single negative tells us very little. The more often the same reaction occurs, the more valuable becomes this negative finding.

If opportunity is afforded to repeat these tests once a month and if there is no variation from third inhibitive and negative fixation in successive

tests, then my previously assumed opinion regarding the presence of tuberculosis is materially shaken.

I may say (here) that the originator has now finished five years serial observation in seventy clinically normal medical students.<sup>9</sup>

Point 4 If in addition to a second-class inhibitive a positive fixation is obtained, the probability of tuberculosis is changed to one of presumability.

Point 5. Slight variations from the normal negative fixation have little influence on the diagnosis of no tuberculosis. Positive fixations indicate the presence of tuberculous disease or that the individual has been recently tuberculous, and that he is yet reacting to tubercle, though it may not be clinically demonstrable.

Point 6 Negative inhibitives in the adult are in themselves suggestive especially if repeated or if devoid of laboratory error, if accompanied by positive fixations, they lend material support to the diagnosis of tuberculosis and with a strong positive fixation are still harder to ignore.

Point 7 In a positive reaction, viz., first or second class inhibitive, we feel safe in assuming, as stated above, that tubercle is a biological, if not a clinical factor, and also that in the majority of cases if given the opportunity we can demonstrate tuberculosis later.

In a small percentage we have not been able to demonstrate the disease. This you will agree is to be expected, in that they make their own cure occasionally, before they would manifest it clinically. You must be reminded that Caulfeild has consistently said that marked inhibitive reactions never necessarily mean clinical tuberculosis.

Point 8 Ten years ago Caulfeild drew my attention to abnormal serological reactions in contacts Since then I have made observations on several hundred cases Variations from negative fixation to straight positive occur in those exposed to massive infection with open cases Abnormal inhibitives also frequently obtain This indicates only biological tuberculosis and precedes clinical tuberculosis, unless these patients have sufficient immunity to succeed in overcoming a biological attack.

Point 9 Marked inhibitives and positive fixations tend to fade out as tuberculous disease disappears, the former usually being the first to fall while the latter may obtain for years

In the 'cured' we believe these reactions are absent

Point 10. Comparing the value of the inhibitive test with the fixation in clinical application, we agree with Caulfeild that *the inhibitive is definitely the more valuable* At the same time, we would not be without the fixation, particularly if we are looking for a diagnosis and if only one blood has been tested

For instance, with only one or two successive tests, we may find nothing more than variations in the fixation This would encourage us to repeatedly test the blood to discover whether any strong inhibitive reactions occur In this way variations in the fixation give us rather a lead or a suggestion than a diagnosis "

EXAMPLES—I shall give ten examples of the tuberculosis suspects class in which serology was of greatest value It will be noted that I

have deliberately chosen cases in which at first examination and survey no positive diagnosis could be made by examination of sputum or discharges and when obtainable, stereo-roentgenograms.

Of the ten cases, eight gave a strong lead towards tubercle by positive serological reactions Of these eight, four later showed tubercle bacilli in the sputum, three showed definite X-ray lesions in the chest and one showed a caseous tuberculous lesion at autopsy The remaining two of the ten examples gave a strong lead against tubercle by repeated negative serological reactions In both of these a satisfactory diagnosis other than tubercle was finally made.

Case 1 (S H dietitian) Detroit Hospital, grippe and basal bronchitis June 1928, unsatisfactory convalescence, referred home for observation and rest Stereos by Dr Ruschlander, Harper Hospital, Detroit, showed diffuse abnormal shadows left base Stereos a month later by Dr W C Kruger, Toronto Western Hospital, showed these abnormal shadows largely cleared T C F positive in three tests during next two months, because of which I urged greater efforts to procure sputum Tubercle bacilli found twice and several times following year at Queen Alexandra Sanatorium under Dr F H Pratten

Case 2 (Mrs Bau graduate nurse) three years observation as tuberculosis suspect, five successive double serological reactions negative—Caulfeild's Inhibitive and the T C F April 1924, I referred her as probable goitre, B M R 118%, operation by Dr R V B Shier Pathological report "diffuse hyperplastic goitre with slight colloid retention" Dr W L Robinson, Toronto General Hospital

Case 3 (Mr P) Feb 1920 patient said diagnosis of tuberculosis made and tubercle bacilli found at Minneapolis P S and stereos scarcely suspicious Caulfeild's In-

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# The Problem of Syphilis in a Tuberculosis Clinic\*†

By ALVIS E GREER, M D., F A.C P., *Houston, Texas*

**T**HIS report of the incidence of syphilis in a tuberculosis clinic is intended to deal primarily with the problem of the presence of syphilis in any form and not with the problem of pulmonary syphilis per se. The position is taken herein that the evidence found as to the presence of pulmonary syphilis is insufficient to warrant the making of such a diagnosis in any of the cases in our series. However, some attention has been given in this paper to the subject of pulmonary syphilis as reflected in the present-day literature.

Before the complement-fixation test for syphilis became generally used, it was the opinion of physicians that syphilis of the lungs was exceedingly rare, whereas, since the complement-fixation test has become more widely used, there seems to be an increasingly prevalent idea among clinicians that syphilis of the lungs occurs more frequently than was formerly thought. There is a marked variation between the clinical impression of the prevalence of lung syphilis and the opinion gained from autopsy findings. This difference of opinion may be explained

in that the tendency of the pathologist to diagnose tuberculosis in preference to syphilis is because he is loath to diagnose syphilis unless treponemata can be demonstrated in the pathologic sections. There seems to be some hesitancy on the part of the pathologist to adequately differentiate histologically between a gumma and a tubercle when it is found in the lungs. As syphilis of the lungs has been presumed to be rarer than tuberculosis, there is a tendency to decide in favor of the commoner lesion, tuberculosis.

Howard estimated in 1924 that there were 200 cases of pulmonary syphilis reported in the literature. Osler has reported syphilis of the lungs occurring only 12 times in 2,800 autopsies at the Johns Hopkins Hospital, 8 of these cases being of the congenital type. Funk found the condition 4 times in 1,200 cases. Howard diagnosed syphilis of the lungs in 7 cases out of 11,982 general hospital admissions. Brock reports finding that 35 per cent of 7,660 consecutive South African negroes had a fibroid condition of the lungs, due to syphilis, among a population, however, of which 80 per cent showed some evidence of syphilis. Out of 3,000 autopsies at the Massachusetts General Hospital, Lloyd found only 1 case of acquired pulmonary syphilis. Between

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†From the Houston Anti-Tuberculosis League Clinic, Houston, Texas.

the years of 1908 and 1923, at the Massachusetts General Hospital, there were 5 cases of pulmonary syphilis recorded. Between 1903 and 1916, the out-patient department of the Massachusetts General Hospital recorded 8 cases of pulmonary syphilis, while in nearly 5,000 autopsies at the Massachusetts General Hospital, pulmonary syphilis was found only in 1 instance. Watkins, from the roentgenological viewpoint, reports that in 6,500 cases syphilis of the lungs was diagnosed in 169

Habliston and McLane, in reviewing the anatomical diagnoses in 2,860 autopsies from the combined services of the Baltimore City Hospital, found evidence of visceral syphilis demonstrated in 309 cases; 5 anatomical diagnoses of syphilis of the lungs had been made, and one of these cases was a congenital one. Landis, Funk and Gibbs are of the opinion that syphilis of the lungs occurs more frequently than is diagnosed. Landis reported 3 cases from the records of the Phipps

Institute and 2 cases from the White Haven Sanatorium. Funk found 4 instances in 72 non-tuberculous lesions of the chest, and Gibbs reported 7 cases of pulmonary syphilis. The diagnosis of pulmonary syphilis in the above report was suggested largely by the occurrence of a positive Wassermann reaction and, further, because the cases were given a therapeutic test on specific treatment and showed marked improvement in their symptoms and pulmonary findings. In this connection, it is suggestive that Barlaro has reported 3 cases of advanced pulmonary tuberculous disease which improved under antisyphilitic treatment. Funk states that Watkins has affirmed that syphilis of the lungs is not as rare as is ordinarily believed.

The coexistence of syphilis and tuberculosis has been noted quite frequently, as would naturally be expected, because of the widespread occurrence and rather universal prevalence of the two diseases. Table 1 taken from Hollander and Narr, who

TABLE 1

Investigation	No of Patients	No Positive	No Probably Syphilis	Pos Percentage	Total Percentage
Lettule, Bergeron and Lepine	346	64	—	19 0%	19 0%
Vedder	211	36	17	17 0%	23 2%
Snow and Cooper	290	44	14	14 0%	20 0%
Lyons	471	29	12	6 2%	9 2%
Jones Dispensary	251	—	73	—	29 0%
Jones Hospital	189	18	—	11 0%	25 0%
Petroff	376	—	82	—	21 8%
Ford	328	6	22	2 0%	8 0%
Collectanea	175	14	9	8 0%	13 1%
Cooper	2794	181	—	6 5%	6 5%
Day and McNutt	893	102	107	11 3%	28 1%
	6324	494	336	10 36%	17 81%

quote from Vedder, Day and McNutt, shows the coincidence of tuberculosis and syphilis very clearly

The diagnosis of pulmonary syphilis has generally been made on the basis of the Wassermann test, the evidence of syphilitic disease elsewhere in the body, repeatedly negative sputum analyses for tuberculosis, and the great improvement of the patient under specific therapy. From the table 1 it is to be noted that 2 per cent and 19 per cent represent the two extremes of the association of syphilis and pulmonary tuberculosis, and that the average is 10.36 per cent.

Pathologically, syphilis of the lower respiratory passages has been quite thoroughly classified. Syphilis of the trachea and bronchi, according to Conner, has four main types, as follows:

- (1) Gummatous swelling of the trachea or bronchi, which swellings may be either circumscribed or diffuse throughout;
- (2) Ulcerations, which occur singly or multiple, and with all possible variations;
- (3) Endotracheal, connective tissue newgrowths which are seen either as distinct scarring or a diffuse thickening,
- (4) Fibrous peritracheitis, occurring as masses of dense fibrous tissue, developing outside the cartilaginous ring.

Lesions of the lungs proper, in acquired syphilis, may occur in one or more of three forms

(1) As a diffuse or local induration, which appears as an interstitial process, observed particularly in the peribronchial and interlobar connective tissues, which runs through the lungs from

the hilus to the base in the form of strands. There seems to be a tendency for more of this to occur on the right than the left side, and the indurative lesion is usually associated with bronchiectatic areas, caused by obstruction of the bronchi.

(2) As gummas, which are less frequent than the indurative type of syphilitic lesion in the lungs, and when found are usually associated with indurated lesions. The gummas occur as masses, which vary in size from tiny nodules up to the size of an egg, and are usually situated near the hilus or in the lower lobe, and are always associated with marked fibrous tissue proliferations. In the course of time the gummas degenerate and caseate, and later become replaced by firm scar tissue. In this way large bands of connective tissue may be seen to run throughout the lungs. Because of the fact that the masses of connective tissue compress the bronchi, a rather general and diffuse bronchiectasis results. Occurring at times in the gummatous form of pulmonary syphilis, and almost always with the indurative type, it is seen that the walls of the blood vessels are thickened and the blood vessels become obliterated. From this condition the pulmonary circulation may be seriously hampered, because of the extensive fibrosis, and the right side of the heart may become considerably enlarged. However, it must be stated that extensive fibrosis throughout the lungs is not definitely pathognomonic of syphilis.

(3) As a gelatinous pneumonia or the so-called "white pneumonia." This condition is evidenced by considerable desquamation of the alveolar cells and

a generalized induration of the lung. The lungs are large, firm and white. Microscopically, the alveolar epithelium is found to be cubical in form, and the alveoli are filled with desquamated epithelial cells, a few leukocytes and a few mononuclear cells; the alveolar septa are greatly thickened, and there is marked proliferation of connective tissue about the bronchi and blood vessels, the walls of which are greatly thickened and their lumens obliterated.

During the secondary stage of syphilis there may be a rather generalized catarrh of the tracheal and bronchial mucous membrane and some increase in the hilus and lymphatic glands.

#### SYMPTOMS OF LUNG SYPHILIS

In the congenital form of lung syphilis the patient is born dead or dies shortly after birth and, therefore, there are no special symptoms characteristic of the pulmonary disease per se. In the secondary stage of syphilis there is a moderate degree of bronchial catarrh with some cough and slight mucopurulent expectoration, due to syphilitic lesions of the bronchial mucous membrane. In the tertiary stage there are no definitely characteristic symptoms of lung syphilis. It is usually assumed that the disease is presumably present when tuberculosis is either partially or wholly excluded, a positive Wassermann test has been obtained, the sputum has been repeatedly negative for tubercle bacilli, and the correctness of the diagnosis tested by definite improvement under specific treatment for syphilis. Lung syphilis is more commonly found in the middle and lower portions of the lungs, leaving the apices free. This is not always

the case, however, as the disease has been found, at times, involving the apices of the lungs. As a rule, gummas are found near the hilus or in the middle or lower portions of the lungs.

The presence of slight deterioration in health, with fever over a long period, the constant absence of tubercle bacilli in the sputum, associated with marked dullness over the lungs, either locally or diffusely, with considerable decrease in the lung sounds and relatively few râles, point suggestively toward the possibility of pulmonary syphilis. Symptomatically, the disease occurs in the acquired tertiary stage as a subacute form which simulates ulcerative phthisis, and, secondly, as a chronic form similar to the fibroid type of pulmonary tuberculosis.

In the subacute form of pulmonary syphilis, there is found considerable dyspnea, a moderate degree of fever, less marked than in pulmonary tuberculosis, a moderate degree of loss in weight and strength, and a fair amount of cough and cyanosis. Hemoptysis is relatively infrequent.

In the chronic form of pulmonary syphilis there may be comparatively few symptoms, presenting only a moderate cough with slight expectoration, with moderate deterioration of weight and strength. However, it is in this type of chronic pulmonary syphilis that there is considerable induration throughout the lungs, that bronchiectasis frequently develops, and because of which there may appear the physical signs of cavitation. The sputum may become putrid, and the patient may develop an irregular septic temperature and become markedly emaciated and sick. It is to be emphasized that there



is a tendency towards less cough, less fever and less deterioration in weight and strength than is usually found in pulmonary tuberculosis. The disease runs a more protracted course than the average case of pulmonary tuberculosis. Fowler gives the following differentiation between pulmonary tuberculosis and pulmonary syphilis

"(1) Tuberculosis usually affects the apex of the lung and subsequently the apex of the lower lobe, and tends to progress in a certain route. The primary lesion of pulmonary syphilis is often about the root and central part of the lung, and the disease follows no definite route of march, and gummas may be found in any position

"(2) Both tuberculous infiltrations and gummas may undergo necrosis and caseation or fibrous transformation, but with the caseous tubercle the tendency towards softening and cavity formation is the rule, whereas a caseous gumma rarely breaks down

"(3) The progressive destruction of the lung by a process of disintegration, leading to a gradual increase in the size of a cavity, a change so commonly observed in tuberculous disease, is rarely if ever observed in syphilis, except as a secondary result of stenosis of one of the main bronchi

"(4) In nearly all cases of advanced destruction of the lungs, occurring in the subjects of syphilis, stenosis either of the trachea or of one of the main bronchi is present, whereas the lesion is very rare indeed in tuberculosis

"(5) The cavities found in cases of pulmonary syphilis are usually bronchiectatic but not invariably so, whereas, in tuberculosis they are commonly

due to progressive destruction of the lung but may be bronchiectatic

"(6) The tendency to the formation of pulmonary aneurysm, which is so marked a feature in tuberculosis, is rarely observed in pulmonary syphilis

"(7) Pulmonary lesions in tuberculosis are very common, whereas in syphilis they are extremely rare"

The diagnosis of pulmonary syphilis rests mainly upon a history of syphilis, the repeated absence of tubercle bacilli in the sputum, the presence of syphilitic manifestations elsewhere in the body, the absence of toxic symptoms commensurate with the degree of pulmonary changes, and a positive Wassermann reaction, and by the improvement of the general symptoms and the local manifestations of the disease under specific therapy

In our investigation of 1944 patients the diagnosis of syphilis was made by the complement-fixation test. Two hundred and forty-two positive Wassermann reactions were found in these cases, 191 cases showed four plus positive reactions, 22 cases showed three plus reactions, 26 cases, two plus reactions, and 3 cases, one plus reactions. In many cases, the Wassermann reaction was checked by the Kahn test. It may be argued that the three, two and one plus Wassermann blood tests should be excluded, but it is not within the scope of this paper to discuss the relative value of a three, two or one plus Wassermann blood test in the diagnosis of syphilis. The discussion is concerned wholly with the cases which showed any evidence of the disease

In studying table 2 it is to be seen that 51 per cent of the total number of

TABLE 2—SHOWING PROPORTION OF CASES WITH TUBERCULOSIS IN THE DIFFERENT RACES

Total number of patients examined	1944
Caucasians examined	1279
Negroes examined	298
Mexicans examined	367
Tuberculous cases	982
Non-tuberculous cases	962
Caucasians	630
Tuberculous	649
Non-tuberculous	
Negroes	160
Tuberculous	138
Non-tuberculous	
Mexicans	192
Tuberculous	175
Non-tuberculous	

patients examined received a diagnosis of pulmonary tuberculosis. In the two races, namely, the negroes and the Mexicans, in which we would expect to find the greatest amount of syphilis, the relatively largest percentage of tuberculosis of the lungs was found

It is interesting to note in table 3 the relatively greater number of positive Wassermann reactions in the tuberculous patients, contrasted with its presence in the non-tuberculous individuals This is especially striking when it is remembered that there were

962 non-tuberculous cases and 982 tuberculous cases examined Although the tuberculous and non-tuberculous cases were almost equal in number, it is seen that the total number of positive Wassermann tests in the tuberculous cases was 156, whereas in the non-tuberculous only 86 cases showed a positive reaction

In table 4 it is to be emphasized that no effort is made to give the symptoms enumerated as those of pulmonary syphilis It is my intention to merely record the symptoms complained of in

TABLE 3 —CONTRASTING THE PRESENCE OF THE POSITIVE WASSERMANN REACTION IN TUBERCULOUS AND NON-TUBERCULOUS PATIENTS

	No Positive Wassermann Reactions
Caucasians	
Tuberculous	61
Non-tuberculous	38
Negroes	
Tuberculous	63
Non-tuberculous	29
Mexicans	
Tuberculous	32
Non-tuberculous	19
Total	
Tuberculous	156
Non-tuberculous	86

TABLE 4—SYMPTOMS OF 86 NON-TUBERCULOUS PATIENTS WITH POSITIVE WASSERMANN TESTS

1 Cough and expectoration	
(a) Dry	30 cases
(b) Productive	28 cases
(c) Bloody	9 cases
2 Loss of weight averaging 10 pounds	39 cases
3 Fever, afternoon type—99°-101° F	53 cases
4 Night sweats	21 cases
5 Pam in chest	57 cases
6 Weakness (moderate)	70 cases
7 Dyspnea	46 cases
8 Hoarseness	36 cases

the 86 non-tuberculous cases which gave a positive Wassermann test for syphilis. It is not to be assumed, necessarily that any of these patients had pulmonary syphilis; many of them showed no abnormal signs on physical examination, except a few scattered râles throughout the chest. The majority of the patients received anti-syphilitic treatment and recovered rapidly of their symptoms. In two cases only did I feel justified in making a diagnosis of pulmonary syphilis, which diagnosis was made on the basis of repeatedly negative sputum analyses, a positive Wassermann blood test for syphilis, and the clearing up of symptoms under specific therapy. Space will not permit a detailed report of these two cases. I cannot help but believe, however, that more of the 86 non-tuberculous patients probably had pulmonary syphilis.

Table 5 shows clearly that, in the series of 1944 patients examined, there was a larger percentage of positive blood tests for syphilis in the tuberculous than in the non-tuberculous cases, a positive Wassermann test being present almost two times more frequently in the tuberculous cases than in the non-tuberculous ones.

TABLE 5—PERCENTAGES OF PATIENTS SHOWING POSITIVE WASSERMANN TEST

Total cases examined (1944)	12.4%
Caucasians examined (1279)	7.7%
Negroes examined (298)	30.9%
Mexicans examined (367)	13.8%
Tuberculous cases (982)	15.8%
Caucasians (630)	9.7%
Negroes (160)	39.3%
Mexicans (192)	17.2%
Non-tuberculous cases (962)	8.9%
Caucasians (649)	5.8%
Negroes (138)	21.0%
Mexicans (175)	10.8%

Syphilis is seen to be especially frequent in the tuberculous negroes and in the tuberculous Mexicans.

In table 6 it is noteworthy that there were considerable evidences of improvement in the tuberculous cases.

TABLE 6—RESULT OF TREATMENT FOR SYPHILIS

1 In the tuberculous cases	
(a) Number treated	33
(b) Result	
Improved	27
Unimproved	4
Dead	2
2 In the non-tuberculous cases	
(a) Number treated	31
(b) Result	
Improved	30
Unimproved	1
Dead	0

treated. Incidentally, it may be said that the treatment consisted largely of the use of neosalvarsan and mercury. In the fatal tuberculous cases, I am under the impression that death was greatly hastened by the treatment, as the patients became rapidly worse after it was begun and died soon thereafter.

#### COMMENT

As has heretofore been emphasized, it is not my purpose in this investigation of only 1944 cases, to attempt to draw any definite conclusions whatever. If this brief study will call attention to the possibly greater prevalence of syphilis in tuberculous patients than is generally acknowledged, we shall feel well repaid. The cases were checked by roentgenological examination of the lungs, repeated sputum analyses, and the complement-fixation test for syphilis. The tests were made on patients, applying at a clinic for diseases of the chest, and who usually presented the symptoms of cough, loss of weight, afternoon fever and weakness.

David L. Belting has given the statistics of thirty-two authors in different cities of the United States and Europe, showing 8.49 per cent of 21,257 patients were infected with syphilis, however, he did not limit his investigation to cases of pulmonary disease only. Pusey has stated that 5 per cent of all male adults and 1 per cent of all female adults have syphilis, which would mean that more than 3 per cent of the entire adult population

of the United States has syphilitic disease. In my study it was found that 12.4 per cent of all the patients examined, whether tuberculous or not, had syphilis, this percentage, of course, was higher because one-third of the cases was made up of negroes and Mexicans. The percentage of positive Wassermann reactions in the total Caucasians examined (7.7 per cent) is practically the percentage given by Belting for the incidence of syphilis in the United States and Europe. One of every three negroes and one of every seven Mexicans showed evidence of syphilis. A positive Wassermann test for syphilis was found to be present 60 per cent more frequently in the tuberculous Caucasians and Mexicans than in the non-tuberculous Caucasians and Mexicans, the Wassermann test was found to be positive more than two times more frequently in the tuberculous negroes than in the non-tuberculous negroes. It is our impression that some of these cases had pulmonary syphilis and we hope to follow them long enough in the future to arrive at an opinion regarding that problem. At least we believe we may infer that the presence of syphilis renders a patient more liable to the development of pulmonary tuberculosis.

I am greatly indebted for the cooperation of my associate, Dr Chas E. Eversberg, and Miss Emmeline Renis, executive secretary of the Houston Anti-Tuberculosis League, in this study.

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# The Use of Sodium Ricinoleate in Bacterial Hypersensitiveness of the Intestinal Tract: Clinical Results

By ROGER S MORRIS, M D, and STANLEY E DORST, M.D.,  
*Cincinnati, Ohio*

IN previous communications,<sup>1,2</sup> we have shown that sodium ricinoleate is capable of rendering bacterial antigens non-toxic. As evidence of this, we may cite the fact that an antigen which, when injected intradermally, produces a marked local reaction, is no longer capable of producing such reaction after treatment with ricinoleate. Larson<sup>3</sup> was the first to demonstrate this detoxifying action while working with the pneumococcus.

Among our private patients, we had encountered a large group, ranging from cases of chronic constipation to mucous colitis, in whom treatment had proved very unsatisfactory. Wherry<sup>4</sup> had shown that the intestinal tract may contain organisms to which the patient is highly sensitized, as shown by intradermal tests. With this work in mind, we began our treatment by administering castor oil daily, hoping that the conversion of the oil into ricinoleates in the intestinal tract might have a beneficial action through its detoxifying effect. The results were so encouraging—and the daily use of

castor oil so distasteful to patients—that we had prepared for our use five-grain globules of sodium ricinoleate.\* These capsules, taken three times a day before meals (and often a fourth at bedtime), we substituted for the castor oil, with even better results.

The treatment which we administered to a group of seventy patients consisted in the administration of the capsules of sodium ricinoleate, as mentioned above, and, in the great majority, we also used an autogenous vaccine which was administered daily. All other forms of treatment, such as diet, colonic flushings, etc., were purposely omitted, to avoid confusion in the interpretation of results.

The symptoms of which our patients complained were varied, being those attributed to so-called "intestinal auto-intoxication." Many had had operations on appendix or gall-bladder without relief of symptoms.

Pains in various parts of the body were frequent. Headache, neuralgic pains in the extremities, abdominal pains usually associated with gas, were common complaints. As a rule, the patients experienced marked relief within a few days after beginning treatment, and in many there was a cessation of the pain. In the patients

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\*These capsules, made by the William S Merrell Company, and designated "Soricin", may be had in five-grain and three-grain sizes, the latter being used chiefly with children.

with severe headache, the effect was perhaps most noticeable. The severe crises of abdominal pain so often seen in mucous colitis were most strikingly affected in those suffering with this disease.

Lassitude and fatiguability were very common symptoms. Neutralization of the intestinal poisons and vaccination usually relieved them.

Distress from excessive gas formation occurred in the majority of our patients. We had previously tried to combat this by the use of lactose and *Bacillus acidophilus*. Our results in the present series of cases were much better than those which we had obtained previously. Patients stated at times that, if they had failed to continue the treatment for two or three days, they were reminded of their omission by a recurrence of excessive gas in the intestines. Many of our patients had also noted a very foul odor of the stools and had stated that this disappeared after treatment was started, in most instances.

Sodium ricinoleate, in the dosage of fifteen or twenty grains daily, has only a mild, if any, laxative effect. For the treatment of this symptom we depended for the most part on castor oil, though in some cases when there was a marked aversion to castor oil, we employed other drugs.

In the patients with mucous colitis, the effect of treatment was very striking. In addition to relieving

them subjectively, there was a noticeable decrease in the mucus in the stools and finally an absence. In the one patient where mucus and abdominal distress returned while under treatment, a malignant neoplasm of the intestine was found and excised. Since the operation the patient has continued to obtain relief.

Anorexia, loss of weight, belching were often favorably influenced by treatment of the intestinal tract. There was not infrequently a gradual gain in weight, with a feeling of well-being, and a relief of the dyspeptic symptoms. The patients were able to play golf or carry out exercises which fatigued them formerly.

In this group of seventy patients, thirty were entirely relieved of their symptoms. In the forty patients remaining, the majority experienced great relief, though not entirely rid of symptoms. Whether patients may be permanently cured remains to be determined. In the cases of mucous colitis, it has been necessary to use the ricinoleate capsules indefinitely, and in all patients of this group there is a great tendency to recurrence of symptoms. This is in all probability due to the fact that the causative organisms cannot be removed from the intestinal tract, but remain a constant menace to the health of the individual. Recently Kline<sup>5</sup> has reported good results in the treatment of intestinal tuberculosis with sodium ricinoleate.

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## Editorial

### *THE NEWER THERAPEUTIC ATTACK ON CANCER\**

The therapeutic attack on cancer is faced at the very outset with what seems to be an insurmountable barrier to its success, and that is shown in the essential nature of cancer itself. Cancer shows no tendency to spontaneous self-healing, as do all of the progressive chronic infective granulomas. Compared with tuberculosis, which in the great majority of cases shows a more or less decided tendency to spontaneous self-healing, there is on record no fully-proved and authentic instance of the spontaneous self-healing of any well-advanced or metastasizing cancer. This fact, in itself, places cancer in a category wholly apart by itself, and should be indicative of its wholly different nature and etiology. Against cancer the body defense mechanisms are apparently powerless. No specific antibodies or immune-bodies are produced by the body of its unfortunate victim. Active immunization against malignant tumors in man does not occur. In the case of the transplantation of animal tumors the only form of immunity that has been shown to exist is a natural resistance to the implanted tumor graft, which is effective only during the first few days following tumor-

inoculation, but is wholly powerless against an established tumor. It apparently is the ability only of certain animal tissues to react against the tumor-graft so quickly and efficiently that the graft is overcome before it obtains a foothold in the new host. Once it begins to grow in the latter, this natural resistance or refractoriness, is no longer potent. Therefore, it seems proved beyond all doubt that an absolute immunity towards cancer-cell proliferation and progressive growth does not exist in the animal body, and that the outcome of inoculation is determined only by the natural protective forces against foreign-bodies and the proliferative vigor of the implant. This generalized refractory state is wholly distinct from other forms of active immunity, it is not passively transferable through the body fluids. Cancer-therapy must then reckon with the fact that it will receive no support or aid from the natural protective and curative powers of the body.

One of the earliest and most primitive facts established regarding the biology of cancer is that in its inception, cancer is a *localized* pathological process, and that if all of the cells of the local growth can be removed before metastasis has occurred, a cure can be accomplished. Upon this primitive foundation fact all of the theoretic and practical views concerning the nature and etiology of cancer, and

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its therapy, as well, are based, and have hardly been advanced beyond these during the last thirty years of the most intensive cancer research and study. What advance has been made in this direction has been the greater emphasis laid upon *earlier diagnosis* and *earlier and more complete operation*. In countless numbers of cases complete and lasting cure from malignant disease has been accomplished through these measures; and the percentage of cures stands in direct relationship to the diagnostic ability and the operative skill of the surgeon. Many believe that these are the only practical therapeutic criteria for cancer, and all cancer propaganda emphasizes their prime importance.

All theories and views as to the etiology and nature of cancer fall into two groups. the *exogenous* or *irritation* theory, and the *endogenous* or *biocellular* theory. Of the exogenous theories that of irritation through specific infection has during the past thirty years received the greatest degree of attention from the clinician. Numerous investigators have also expended enormous amounts of energy and labor in the effort to find a specific infective etiologic agent for cancer. Every possible variety of organism, microbic, yeast, mould, and protozoan, have at one time or another been made to contribute some species incriminated as the cause of cancer, but all to no avail. Even in those infectious diseases more or less definitely associated with the development of malignant tumors, as the Spiroptercarcinoma of the rat stomach, the cysticercus sarcoma of the rat's liver, and the Bilharzia carcinoma of man, not

the slightest idea of a specific causal relation of the parasite to the associated tumor can be entertained, inasmuch as the parasites are usually dead before the development of the neoplasm, and moreover, are never found in the metastases, nor in the transplants of such tumors. In spite of the overwhelming evidence against the theory of the specific infective etiology of cancer there still arise from time to time individual workers who support it. Most of them base their belief upon the Rous chicken-sarcoma and its hypothetical filtrable virus assumed to be a living virus. This tumor, which has enjoyed a certain vogue of distinction on the ground of being at least one malignant tumor due to infection, has hindered the path of progress as far as the etiology and essential nature of neoplasm are concerned. Apparently recent workers have shown conclusively that the virus is not a living one, but a chemical substance of the nature of a growth ferment or biologic catalyst, influencing cell reproduction; and the hypothesis that the potent agent in the filtrate of the Rous sarcoma is a sub-microscopic organism has now been abandoned by most of the workers engaged in cancer research. All therapeutic attempts based upon the theory of a specific infective agent for cancer have resulted wholly in failure, vaccines, serum treatment, etc., have yielded no results either in human beings or in the case of animals.

With the abandonment of the old hypothesis of specific infection the cellular or endogenous theory has come to be more and more in the ascendant. This theory maintains that the essen-

tial nature of cancer lies in the cancer-cell itself, and that the cancer cell is a specifically changed cataplastic cell, whose individual character is to be sought wholly in specific changes of its living structure. Proof of this theory has been accumulating almost from day to day, and we have already acquired a large amount of knowledge concerning the characteristic chemical and physical properties of the cancer cell. These characteristic deviations of cancer cells from the normal show themselves in their transplantability to other individuals, their power of continued growth in cultures outside of the animal body, even in heterogenous serum, in their ability to destroy normal cells in cultures, and in their metabolism. Warburg has shown that the tumor cell has a pathological sugar metabolism, which manifests itself by a lessened oxidation, and an increased fermentation (glycolysis), especially in the presence of oxygen (aerobic glycolysis). Both methods of carbohydrate metabolism are found in all tissues, but in cancer tissue glycolysis is excessive, with the production of large quantities of lactic acid, which accumulates in a manner not found in normal tissues. This glycolytic capacity of tumor cells enables them to survive under anaerobic conditions. Brerich has repeated Warburg's work and argues with him that there is an unusual accumulation of lactic acid in cancer tissue. He, however, explains this lactic acid excess as due to the inability of the cancer cell to re-synthesize the acid to glucose, rather than to its rapid formation. Brerich regards the excess of lactic acid in cancer as a mechanism whereby cancer

tissue is able to destroy the normal connective tissue about the growth and thus aid in the dissemination of the cancer. According to recent investigations of Waldschmidt-Leitz, the increased proteolysis of the cancer cell is coupled to this increased glycolysis. Cancer research at the present time has become largely biochemical and is concerned with the biology of cancer, its essential nature, cataplasia, metabolism, and heredity. The great problem is how is it that normal cells become altered to cancer cells, how does the specific cancer cell arise in the body? All agree that they do arise from body cells. In seeking a biologic answer to this question, only two biologic processes stand out as definitely related to those involved in the genesis of tumor formation, and these two are the processes of embryonal and regenerative development. For a large number of neoplasms an embryonal anlage is known with certainty to exist, as for example, in the case of malignant teratomas of the ovary and testis, the malignant neuroblastoma of the retina and sympathetic system, the neoplasms of the adrenals and kidneys in the newborn, the chordoma, angiomas, hereditary multiple chondromas, branchiogenic carcinomas, familial intestinal polyposis, and many other neoplasms, whose origin is to be referred to embryonal disturbances of development. Besides these neoplasms of undoubted embryonal origin are the tumor-formations which are *acquired* and not of embryonal origin, as x-ray cancer, paraffin cancer, arsenic carcinomas, mineral oil cancers, tar cancers, Billharzia carcinoma, kanger cancer, and carcinomas arising in old scars, and a

whole series of neoplasms in which any local congenital anlage can be positively excluded. On the basis of both experimental investigations and many clinical observations on acquired malignant neoplasms in both man and animals, we can come only to the conclusion that these acquired neoplasms owe their origin to a repeated and frequently disturbed pathologic regeneration. Not every disturbance of the processes of regeneration leads, however, to the development of neoplasm. The recent researches on the experimental production of tar and arsenic cancer show that long-continued action of the carcinogenic substance leads to a gradually increasing disposition to the formation of a neoplastic center out of the area of regeneration. Further, it has been shown that two essential factors are necessary to tumor-formation, a general tumor-predisposition, which may be confined to one organ system, and secondly, a local tumor germinal anlage. Both of these may be embryonal or inherited, leading to the development of the typically congenital or inherited neoplasm. Both factors may also be acquired, or one may be inherited, and the other acquired. This view of the genesis of cancer is the one accepted at the present moment by some of the leaders in cancer investigation. These new hypotheses and views concerning the essential nature of cancer are reflected in an enormous number of investigations concerning the treatment of cancer. Cancer therapy, as far as its experimental study is concerned, has broken away from the old traditional line of attack, and is entering new and untrodden paths. The amount of re-

search work that has been accomplished is so great that only the briefest analysis can be made of it here.

Particularly extensive and ingenious have been the researches aiming to produce antibodies against the cancer cell itself. As long as 25 years ago Jensen treated mouse-carcinoma with the serum of rabbits injected with the same growth, but without any influence. Borrel tried the same thing in sheep and fowls, but was also unsuccessful. Abderhalden used the expressed juice from a rat-sarcoma, and obtained a serum from rabbits and dogs which he claimed would bring about the gradual disappearance of the tumor in rats, but Fraenkel and Fürer were unable to confirm his claims. Tyzzer, Lewin and Meidner, and Sisto, treating mice, rabbits, and guineapigs with injections of sarcoma and with saline suspensions of various organs of the normal mouse found that the serum of animals so treated was no more active than that of normal ones. Yamigiva and associates have carried out experiments on a large scale, using mouse-tumor as antigen, examining extracts of the spleen *in vivo* and *in vitro* for antibodies without result. Lumsden and Stephen obtained similar negative results without anti-sera. Bogomolets and Neiman have employed a cytotoxic serum with results that are not convincing. The body-fluids of animals that have absorbed their neoplasms have been repeatedly examined for antibodies without result. Fraenkel and Fürer found that subcutaneous or intravenous injection of the press-juice of tumors had no curative effect upon rat-sarcoma or mouse-carcinoma. The intraperitoneal intro-

duction of mouse embryos and placenta, of embryo skin, and of spleen had no influence upon transplanted tumors. Heated tumor has been used as a therapeutic agent against rat-sarcoma by Serafin, mouse-carcinoma by Takahashi, and chicken-sarcoma by Berger, without encouraging results. Tumor autolysates have been used by Blumenthal, Hirschfeld, and Lewin, who claim moderate success, but numerous other workers have failed to duplicate their results. Glycerine extracts of various organs of heterologous species were all ineffective against mouse-carcinoma. Raising the temperature of tumor-bearing animals, repeated chloroform anesthesia, and the use of lactic acid have all been found to have no effect upon the stock animal transplantable tumors. Human patients have been treated by Kawakami, Nakamuri, and Takei, with the serum of horses or goats inoculated with human cancer; Zerner with their own serum; Sticker with radium and cells from their own tumors; Elsner with the serum of young individuals, Fichera with autolyzed tissues, but all without any encouraging results. Tumorzidin, produced by introducing testis, ovary, or embryo, into a heterologous species has been unfavorably reported upon by Deutselmann and Kotzenberg. Okanogi found it ineffective against transplanted mouse- and rat-tumors, even when employed in larger doses relatively than those advised for the human patient. Summing up all of the work that has been carried out along this line, we must conclude that active immunization against malignant tumors in animals or man is not possible.

The attempt to find some substance that would be *lytic* for cancer cells and harmless to the living normal tissue cells has been intensively carried out in animals in various research cancer laboratories, and in man in a number of clinical centers. Almost every known chemo-therapeutic agent has been employed, but without dependable results. Colloidal lead, silver, copper, and gold have been intensively tried out, particularly in the case of lead by Bell and Todd. In general, biologists and biochemists have failed to find any specific action upon cancer cells by the compounds used, and we may sum up this phase of cancer-therapy by saying that a scientific basis for this mode of treatment of cancer is not established. The same thing is true of the application to cancer-therapy of injections of intravital dyes; about 150 various dyes having been tried out by different workers up to the present time without any promising results. The claims of Munck in Copenhagen of the favorable action of trypan blue on transplanted tumors in mice could not be confirmed by other workers. Similarly the work of Bernhardt and Strauch with intravenous injections of isamin blue on cases of human cancer could not be confirmed by Fichera in Milan. Thirty-two inorganic salts were tried out by Sugiura and Benedict; potassium, magnesium, sodium, and calcium by Sano and Mizutani, magnesium chloride by Itami, allyl derivatives by Koenigsfeld and Prauchnitz; iodine, arsenic, antimony, sodium fluoride, naphthalin, selenium, and tellurium by Uhlenhuth; indol products by Centanni; metals and tartrates by Ishinari; nucleic acid and various pro-

tein preparations by Lewin; vitamins by Fraenkel and Fürer, and many other investigators; insulin by Kato and Cioffari, extract of adrenal cortex by Coffey and Humber, and many other substances, all of which yield results not acceptable to conservative criticism. Recently mustard gas (dichlor-ethyl-sulphide) is being exploited by certain English workers as an anticarcinogenic substance. What practical application to human cancer can be made of this does not seem apparent.

Irradiation with x-rays and with radium have enjoyed a marked vogue of popularity in the treatment of human cancer. The most experienced workers, as Regaud in Paris, Fichera in Milan, Blumenthal in Berlin, and Forsell in Stockholm, with others in Europe and in America are agreed that as a primary form of therapy, radium is successful only in cancer of epidermal origin (skin of face, tongue, and female genitalia), and has certain advantages over surgical operation. In other lesions, its use is purely palliative. Combined with surgery the use of radium has a definite but limited sphere of usefulness. Improvements in the technique of radium treatment will undoubtedly extend this.

The newest field of cancer-therapy investigation is based upon the effort to influence the metabolism of the cancer cell. Warburg has carried out a series of experiments on mice with the aim of starving out the cancer cells by interference with their sugar and oxygen supply. In an attempt to interrupt the respiration of the cancer cells the animals were made to breathe an atmosphere containing only 5 per

cent of oxygen over a period of several hours. Apparently because of the over-crowding of the cancer-cells and through injury to the cells of the thin-walled blood-vessels of the neoplasm, the tumors were less resistant to oxygen lack than the normal tissues, and biopsies showed that practically all of the cancer cells had died or ceased to function. Attempts to interfere with the sugar supply of the tumors by maintaining the animals in insulin shock did not appear to influence the survival of the tumors. Sokoloff of Prague, has reported experiments in which the cancer cells were injured by an opposite metabolic effect, too rapid breathing, induced by the injection of a compound containing an extract of the adrenal cortex. Other experiments with insulin, vitamins, and metabolic products have up to the present time been fruitless. Jacobson attempted the suffocation of tumors by means of yeast, which split up the glycogen in and about the growth into carbon dioxide and water, but no controls were mentioned and the number of animals employed was too small to admit of any conclusion as to the value of this treatment.

Fischer-Wasels, of the Senckenberg Pathological Institute in Frankfurt, has contributed the latest new method of cancer-therapy on the theory of influencing the general metabolism of the body and that of the cancer-cells themselves, based upon Warburg's theory of the pathological respiration and glycolysis of the tumor cell, and upon the alkalosis of the blood observed in cancer-patients by Reding and others; and upon his own views of the excess of lactic acid in the tu-

mor. Based upon the results of animal experiments, Fischer-Wasels has employed the following treatment of cancer in human beings for 1½ years

*A. Local Treatment* Intensive deep x-ray therapy of the primary tumor, and when necessary, of the metastases, according to the method of Holfelder

*B General Treatment.* 1. Daily 2-4 hours breathing of a mixture of pure oxygen and 5 per cent carbonic acid, with tightly fitting mask to avoid apparent respiration

2 Three times daily, after meal times, HCl per os in largest possible doses (Control of the PH of the urine).

3 Activation of the reticulo-endothelial system by ultraviolet irradiation (Alpine sun) of the entire body The dose to be regulated according to the individual, and to prevent over-loading of the reticulo-endothelial system, the untraviolet irradiation should not be carried out on the same day as the x-ray irradiation.

The number of human cases so far treated by this method is small, largely due to the cost of the gas-mixture, since the treatment must be carried through many months without interruption. Good results are claimed for this treatment in a number of cases of carcinoma of the esophagus, inoperable carcinoma of the stomach, and in a case of carcinoma of the mamma with generalized metastases Less striking results were obtained in cases of cancer of the cervix, uterus, and intestine. The breathing of the gas-mixture was carried out without difficulty and, although continued in some cases for many

months, no harmful effects were observed from it The treatment appeared to produce good effects on sleep, appetite, blood-condition, and weight After each treatment a local painful reaction was observed in all external malignant tumors and bone tumors; and in single cases, also in carcinoma of the uterus and intestine, which were repeated after each gas-breathing The general condition improved, the blood picture became better, the weight increased, and the cancer cachexia was brought to a standstill for months

The results claimed for a series of cases treated by this combination of deep x-ray therapy and gas-acid treatment are striking, but the number of cases is too small to permit any definite conclusions to be drawn. In the meantime experimental treatment of human cases by this method will continue, and the results will be published later. It is encouraging that this new biologic method of treatment, which is developed upon the basis of known facts as to the nature and biology of cancer, is not heralded as a new cure for cancer, but the theory and method are explained in a conservative and scientific manner and no claims are made Further, it is the first method of cancer therapy to be based on the modern biologic and constitutional conception of the etiology and nature of cancer. Whether these theories and their therapeutic applications are right remains to be seen It will take the experience of years before any positive judgment as to the curative value of any form of cancer treatment can be made. The consensus of opinion as to the criterion of cancer cure in the adoption of a

five-year period without recurrence is altogether inadequate, in the opinion of the writer, who has repeatedly seen recurrence after seven, ten, and twelve years. In a case of scirrhus carcinoma diagnosed by him in 1914, the patient was still alive in 1927 with

generalized metastases in the lungs. While such cases are not the rule, yet the possibility of delayed recurrence and metastases constitutes a factor of importance in the evaluation of any supposedly curative method of treatment of human cancer.

## Abstracts

*Further Experiments Concerning Immunologic Reciprocity Between Yaws and Syphilis* By OTTO SCHÖBL (The Philippine Journal of Science, October, 1930 p 263)

Additional experimental evidence showing that yaws infection immunizes Philippine monkeys against cutaneous inoculation with syphilis is given in this paper. Eleven Philippine monkeys that had gone through yaws infection and were proven to be immune to yaws were inoculated with syphilis by intradermal injection on the scrotum. Two normal control animals were included in the test for immunity to syphilis. The shortest interval of time between the first inoculation with yaws and the test for immunity to syphilis was twelve months, the longest twenty-one months. Following the inoculation with syphilis the places of inoculation were inspected regularly for a period of five months. At various intervals of time the inguinal lymph nodes corresponding to the point of inoculation with syphilis on the scrotum were removed aseptically and transplanted to the testicles of normal rabbits. These rabbits were inspected weekly for a period of five months and the results were noted. None of the yaws immune-monkeys developed lesions at the places of inoculations with syphilis, and none of them harbored viable spirochetes in the lymph glands corresponding to the places of inoculation with syphilis. All normal control monkeys developed typical syphilitic lesions and harbored viable spirochetes in the lymph nodes corresponding to the places of inoculation with syphilis. The conclusion drawn from previous experiments that immunity to yaws gained by yaws infection protects Philippine monkeys against cutaneous inoculation with syphilis is hereby confirmed.

*Psittacosis Epidemiological Considerations with Reference to the 1929-30 Outbreak in the United States* By CHARLES ARMSTRONG (Public Health Report, August 29, 1930)

Psittacosis of man has been reported for the United States by Vickery and Richardson, 1904, Scott, 1906, McClintock, 1925, and Sailer, 1927. The 1929-30 outbreak is, however, the most extensive yet reported for this country. Nevertheless, it seems certain that this outbreak would largely have escaped detection as to its real nature had not the press brought the condition and its striking association with parrots before the public and the medical profession. It is, therefore, impossible to determine to what extent the recent outbreak is exceptional, but if we are correct in concluding that the disease is endemic among tropical birds, and considering the frequency with which psittacosis has been reported in other countries, it seems probable that sporadic cases have occurred more frequently in the United States than has heretofore been realized. There are now on record 74 foci of infection which gave rise to 169 cases with 33 deaths, from November 23, 1929, to May 7, 1930. These cases occurred in 15 states and the District of Columbia, and do not include 16 laboratory infections with two deaths, nor 12 probable cases which were removed from two merchant ships entering our ports, following exposure aboard ship to parrots purchased in Germany and Brazil. The mortality in the reported cases was 19 per cent. It is possible, however, that other deaths occurred in this series, since many of our reports were secured prior to the termination of the illness. Age is an important factor in determining the outcome, children and young folk tending to have light attacks. There



was not a death reported among 35 patients under 30 years of age, while approximately 24 per cent of patients over the age died. Death is probably due to the pneumonic involvement in most cases, and occurs usually from the 7-15th day of illness, later deaths, however, occasionally occur and may be due to embolism from a complicating venous thrombus, at least two deaths attributed to this cause occurred among the above-mentioned fatal cases. Theoretically, the control of psittacosis in man is simple and consists in the avoidance of contact with tropical birds. Practically, however, it may be difficult permanently to prevent traffic in birds which are favored as pets by a considerable group of our population. Methods aimed toward rendering the traffic harmless rather than toward preventing it are therefore desirable. Strictly scientific information is, however, not yet available for the guidance of such a plan.

*Die Insulmlipodystrophie bei Kindern* By RICHARD PRIESEL and RICHARD WAGNER (Klin Wschr, Aug 16, 1930, p 1548)

Two years ago the authors noted a local disappearance of fat in insulin-treated children. They came to the conclusion that it was very probable that the local lipodystrophy was due to the trikresol added to the insulin for purposes of preservation of the latter. Depisch (Wien Med Wschr 80, 168, 1930) made observations also on this local lipodystrophy and came to the following conclusions. In about 10 per cent of insulin-treated patients there develops, after 2 months to 2 years, a disappearance of adipose tissue in those skin areas in which the injections have been given. This lipodystrophy is more frequent in the female sex than in the male. It is dependent upon the traumatic-chemical local reaction. Depisch regarded it as probable that the disappearance of the fat was directly dependent upon the use of the insulin and of neurotrophic origin. To avoid its occurrence he recommends the frequent changing of the injection area. Inasmuch as he was unable to produce the condition by the injection of trikresol in a patient for a period of two months, he decided that the insulin itself was the cause of the disappear-

ance of the fat. Priesel and Wagner, on the other hand, believe that the local lipodystrophy resulting from insulin injections is the result of a severe grade of trikresol injury. Mild degrees of lipodystrophy are found in a large per cent of diabetic children, severe forms are rare. They saw two cases only in 109 diabetic children and both of these were boys. In one of these during a period of fat increase in the body the injected area remained free from fat deposit, so that the condition was not one of local fat disappearance but rather one of a lipophobia. Priesel and Wagner recommend the frequent changing of the area of injections in diabetic children, and the use of concentrated insulin. If the tissue-damage was due to the insulin the use of concentrated insulin would be contra-indicated, but its use in one patient in whom lipodystrophy had already occurred, produced no new areas of loss of fat, hence, the author's believe their theory of trikresol damage to be correct.

*Liver and Copper* By N. ANDRIANOFF and S. ANSBACHER (Deut med Wschr, 1930, p 357)

The copper content of the normal liver varies between 0.5 and 13 mg pro Kilo liver. Out of 21 cirrhotic livers only 3 had a copper content under 20 mg, the others had a much higher value, even over 100 mg. Experiments on rats would tend to show that the copper has an etiologic rôle in the production of cirrhosis, and that the increased copper content is not the result of the cirrhosis. Feeding of rats with inorganic copper salts led to the production of a cirrhosis of the liver in three out of 4 cases. The increased copper content of the nursing's liver has no relation to that in hepatic cirrhosis. This finding, demonstrated by Lubarsch in the case of man, was confirmed in the case of animals by these observers.

*Ueber Bang—Infektionem im Kindesalter* By A. HÖRINGER (Klin Wschr, Sept 13, 1930)

The clinical picture of Bang-infections is so little known that it is important to collect and to publish observations on this in-

interesting disease. Whether diseases due to infection with the Bang bacillus are common or rare is a question not yet settled. One has the impression that few cases have been correctly diagnosed because the disease picture is very similar to that of other diseases, and the diagnosis cannot be made through clinical data but by means of bacteriological findings. Bang infections have been described only a few times in children. Fleischmann and Radatz reported a case of the disease in a child of 10 years, and Kling one in an 8 year old. In the American literature there are reports on five cases occurring in the first decennium. One of these was 22 months old, another was only 15 months. Hottinger reports two cases observed by him, which are of interest not only because of their age, but also clinically and from the standpoint of epidemiology. Diagnosis was made serologically. One was an abortive case in a 4 1-2 year old boy with moderate fever, roseolar eruption, and spontaneous healing in a few weeks. The other case was that of a 9 year old girl with a severe, protracted, high fever, with the clinical picture of infective jaundice, and showing a lowered constitutional value following whooping cough. This child had been nourished without milk. The first child also had had no raw milk. The epidemiology of both cases is therefore of the greatest interest. Other milk products, however, may have been responsible for the infection. Butter and cheese had been a part of the diet in both cases. Since raw milk as the source of the Bang infection in these two cases can be wholly excluded, suspicion is thrown upon other milk-products, butter especially, as conveying the infection. Both patients came from the same quarter of the city in which an adult with a severe Bang infection lived, and in the same street in which patient No. 1 lived, dwelt also the milk-dealer who delivered milk to the house of patient No. 2 in Solingen. For over a year an epidemic of febrile icterus had prevailed in Solingen. Whether this was due to a Bang infection is not definitely proved, but the coincidence was suspicious. No positive information could be obtained fur-

ther that would throw light upon the epidemiology. The diagnosis in both cases rested upon the serological findings—a positive agglutination in a dilution of 1:200. In case No. 1 the agglutinating power of the serum became negative after recovery. These two cases show that Bang infections, like other septic processes, may show the greatest differences in the clinical picture.

*Syphilis and Malignant Disease. A Serological Study.* By H. J. B. Fry (The Jour of Hygiene, XXIX, 1930)

There exists some doubt as to the exact importance to be attributed to syphilis in the etiology of malignant disease. Esmarch (1889) believed that malignant disease was referable to a predisposition inherited from syphilitic forebears. Syphilis has also been regarded by French writers as of great importance in the production of cancer, who have termed it "le lit du cancer". Others regard the relationship as less definite. Foerster found only 4 positive Wassermanns in 35 cases of cancer, Caan had positive results in 41 per cent of 85 cases of carcinoma, Fox found 5 positive reactions in 207 cases of cancer. McCormac and Mason in 137 cases of cancer found 10.2 per cent positive Wassermanns. Fry took 1000 unselected cases of malignant disease receiving treatment in the Cancer Hospital, London, and compared the figures of the Wassermann reactions obtained with a control series of patients similarly attending the hospital but found to be suffering with diseases other than malignant. The same method and the same alcoholic extract were used throughout. Harrison's technique was used. No serum was regarded as giving a weak positive unless there was complete (+) or at least partial inhibition of hemolysis in the tube containing 3 M.H.D. of complement. In the latter case the sera were examined on a subsequent occasion or a fresh sample taken. The conclusions arrived at may be summarized, as follows. There is a lower percentage of positive Wassermanns in cases of malignant disease than in a similar population of non-malignant cases. If buccal cancers are excluded, the percentage is half that in non-malignant

nant cases Cancer of the tongue and buccal cavity, in which a high percentage of positive Wassermanns is found, is almost confined to males and is probably due less to syphilitic infection than to some other factor such as smoking There is a low percentage of syphilis in cancer of the digestive tract, except in cases of cancer of the stomach, and the incidence diminishes from mouth to anus Syphilis does not appear to be a factor of importance in cancer of the glandular organs, nor, apart from the lip, in the production of cutaneous cancer In general, from the above figures there is no evidence that syphilis plays any direct or very important part in the production of cancer In the 1000 cases of malignant disease there were 97 positive Wassermanns or 9.7 per cent In 868 controls there were 115 positive reactions or 13.2 per cent

*Probable Cause of Jamaica Ginger Paralysis* (United States Public Health Service, August 20, 1930)

A peculiar form of paralysis, perhaps unlike anything ever known before, has recently afflicted a relatively large proportion of the population throughout some of the Midwestern and Southwestern States Definite figures on the extent of the disease are not available, but it is certain that the numbers run into the thousands At the request of the State Health authorities of several States, the United States Public Health Service undertook studies of this condition The investigations made in some of the stricken areas in Ohio and Tennessee seem to confirm the widespread rumor that the disease is closely associated with the drinking of an adulterated fluid extract of ginger That it could not be due to the ginger as such became clearly evident from the fact that many of the victims when questioned admitted freely of having used similar preparations for beverage purposes for from 1 to 5 years with no other affects

than those derived from the alcohol It soon became evident, therefore, that the condition must have resulted from some unknown poison or from some known poison whose action was so altered through the ginger or the alcohol as to render it unrecognizable, which poison in some way got into a manufactured lot of so-called fluid extract of ginger at a relatively recent date

The possibility of some known or only partially known poison with its properties so altered as to produce a condition in man heretofore virtually unknown, must be considered From the very nature of the problem it would seem not improbable that the suspected ginger contained some denaturant, since denatured alcohol might very well have been, and probably was, used in the manufacture of some of the ginger extract, or that it contained some adulterant, since it is known with certainty that adulterants of various kinds have been used for some years in the manufacture of this preparation The studies conducted by the Public Health Service, though by no means complete, seem to indicate that the latter explanation appears to be the correct one, though the mechanism of the suspected adulterant is as yet not clear

The exact nature of the pharmacology of the compound which has been found uniformly present in suspected ginger and absent in unsuspected ginger is as yet unknown From its chemical behavior it appears to resemble a phosphoric acid ester of Trikresol, which in itself does not appear to be a well-defined chemical entity Its resistance to heat, the strong alkali and extreme heat required for its saponification, and the fact that phosphate has been found in the suspected gingers, would make it very probable that it may indeed be the ester suggested

Further studies of the subject are being continued by the Public Health Service

## Reviews

*The Long Trek* Around the World with Camera and Rifle The Story of an African Asiatic Expedition, 1929-1930 By RICHARD L. SUTTON, M.D, Sc D, LL D, FRS (Edin), Professor of Dermatology, University of Kansas, and RICHARD L. SUTTON, JR, A M, B Sc, M D With more than 200 illustrations, 347 pages. The C V Mosby Company, St Louis, Missouri, 1930 Price in cloth, \$5 00

Those who had the pleasure of reading "An African Holiday" and "Tiger Trails in Southern Asia," Dr Sutton's other travel books, will welcome the present volume with its interesting story of his third hunting trip in East Africa, Sumatra, and Indo-China. This expedition was undertaken in fulfillment of a promise made many years ago to his son, on completion of his medical course, and two of the chapters and more than half of the photographs are contributed by the latter. Their trip proper began at Tanga, thence to Moshi and Arusha, where their hunting actually began. The story of their kills is much less interesting than the tale of their wanderings, with their many observations on the scenery, customs and manners of the natives, and above all the many interesting photographs taken. These in themselves are the best part of the book and give one a better idea of what Africa is really like than pages of description could accomplish. Both of the Suttons are experienced photographers and have an instinct for the picture that is interesting. On these trips thousands of photos and many thousand feet of movie film were taken, and nearly five hundred illustrations were taken from the best of these for use in the three books. From Africa our hunters went to Indo-China in pursuit of tigers, and here fortune was more propitious than it had been in the case of elephants and lions in Africa. In the case of lions, leopards, and tigers, the Suttons proved conclusively that catnip oil

did not attract the animals, but actually frightened them away. The Asiatic elephant proved as wary as the African. The younger Sutton chased a herd for five weeks without getting a shot. On the whole there is less of hunting in this volume than in the other two, but this does not make it any the less interesting as a tale of travel in strange lands. This tale is told with a refreshing vivacity and conciseness, and in a most graphic manner.

*The Candirú The Only Vertebrate Parasite of Man* By EUGENE WILLIS GUDGER, Ph D, Bibliographer and Associate in Ichthyology, American Museum of Natural History, New York City. With a Foreword by ALDRED SCOTT WARTHIN, Ph D, M D, LL D, Professor of Pathology and Director of the Pathological Laboratories in the University of Michigan, Ann Arbor. 120 pages, 18 illustrations. Paul B Hoeber, Inc, New York, 1930. Price in cloth, \$1 50.

For more than a hundred years travellers in the Amazon valley have brought back tales of a fish that has the unpleasant habit of entering the urethra of men and women bathers, particularly if they should pass urine in the water. By erecting spines on its gill covers the fish could so firmly establish itself, that only a serious surgical operation could effect its removal. So widespread among the natives was a belief in this story, that in various Amazonian waters, bathing is not resorted to without the precautionary protection of the genitals by different contrivances, such as cocoanut shells or sheaths made of palm leaves. The late Professor Eigenmann was fully convinced of the truth of these stories, and created the new genus *Urinophilus* to include the fish showing this peculiar habit. The name Candirú is a collective name given to the small catfishes of the Amazon and its tributaries belonging to

this interesting genus Gudger's object in writing about the Candiru was to collect all of the material bearing upon this alleged human parasitism of the Candirú and to present it in definite form with the view of subjecting these accounts to a rigid scientific scrutiny to determine whether or not these tales are credible. This was a task of five years. There is set forth in his book a great mass of testimony bearing on the subject from 1829 to 1929, and this testimony backed by the names of the testifiers is impressive and conclusive. To the material afforded by the literature has been added the experience and testimony of scientific and medical men in Brazil. From the ichthyologist's point of view the evidence has been arranged and analyzed in order beginning with the simplest habits of the fishes and moving steadily up to the matter of parasitism and urinophilism. All of this is told in a vivacious and interesting manner that makes this fish story very good reading indeed. As a biologic phenomenon the acquisition of urethral parasitism by these minute fish possesses the greatest interest as one of the minor evolutionary processes admitting of scientific interpretation. Gudger concludes his interesting story with the statement that the evidence offered is sufficient to convince a jury in a court of law, and that he cannot withhold his belief in it.

*Clinical Examination of the Nervous System* By G. H. MONRAD-KOHN, M.D., F.R.C.P., Professor of Medicine in the Royal Frederick University, Oslo, Physician-in-Chief to the University Clinic for Nervous Diseases, Oslo. With a Foreword by T. GRAINGER STEWART, M.D., F.R.C.P., Physician to the National Hospital for the Paralyzed and Epileptic, Queen Square, Neurologist to the West London Hospital. Fifth Edition. 222 pages, 57 illustrations. Paul B. Hoeber, Inc., New York, 1930. Price in cloth, \$2.50.

The issue of five editions, in addition to a revised French edition, since 1921, speaks well for the reception accorded this clinical manual of routine methods of examination of the nervous system. For the present edition the author has again revised the book,

and has made a number of minor additions and alterations. A short description of the methods of ventriculography and encephalography has been added. In the chapter on repeated examinations the author has also added a description of the uses of hypertonic solutions as a means of reducing intracranial tension and thereby rendering a dazed patient cooperative for a subsequent examination. As in the case of the other editions the present one is not a translation, but was written in English by Dr. Monrad-Kohn himself. The book is therefore free from that vagueness of meaning common to many translations. It is to be recommended to all who are especially interested in disorders of the nervous system, as well as to those engaged in general practice.

*Minor Surgery and Bandaging* For the Use of House Surgeons, Dressers, and Junior Practitioners. By GWYNNE WILLIAMS, M.S., F.R.C.P., Surgeon, University College Hospital. Twentieth Edition. 445 pages, 262 illustrations. F. A. Davis Company, Philadelphia, 1930. Price in flexible covers, \$3.50.

The changes which have been made in the twentieth edition are scattered throughout the book. They are all those which have been practically tested, and which have passed into the ordinary routine of house surgeons, as for example, the injection treatment of varicose veins. The chapters on fractures have been extended, and the non-operative treatment of the common varieties has been detailed more fully with the aid of illustrative diagrams. The chapter on anesthetics has been revised by Drs. Dudley Buxton and H. N. Webber. The material is treated in the following chapters: The Examination of the Patient, Asepsis, Preparation of the Patient for Operation—The Operation, Post-Operative Treatment, Wounds, Contusions, Burns, Accidents, Foreign Bodies, Etc., Hemorrhage, Genito-urinary Diseases, Acute Abdominal Conditions, Hernia, etc., Minor Operations, Irrigation—Ointments—Fomentations—Poultices—Strapping, Bandages, Fractures, Special Fractures, Dislocations, Orthopedic Appliances, The Administration of Anesthetics—Local, Regional, and Spinal Anal-

gesta. The material is thorough and excellent, it is well organized. It will be of great service to internes and house-surgeons as a convenient, handy book of minor surgery.

*The Action of Muscles. Including Muscle Rest and Muscle Re-Education.* By Sir COLIN MACKENZIE, M.D., F.R.C.S., F.R.S (Edin); Professor of Comparative Anatomy, and Director of the Australian Institute of Anatomy, Canberra. Second edition, 288 pages, 100 illustrations. Paul B. Hoeber, Inc., New York, 1930. Price in cloth, \$3.50.

With the rapid development of physical therapy in this country, an increasing amount of attention is being paid to the importance of muscle function, and a department of myology or muscle re-education is now instituted in the majority of modern hospitals. The after-experience of the great war showed that 65 per cent of the wounded men returning from the battlefields were suffering from disabilities of an orthopedic nature of such a character that the question of muscular function became of prime importance for purposes of treatment. Muscular tissue alone constitutes the greater part of most animals, and more attention should be paid to the teaching of muscle function. This cannot be taught satisfactorily in the dissecting room, but should be demonstrated upon the living body, through comparison of the normal with the paralytic. Only on this plan can the question of the origin and insertion of a muscle have more than an academic interest for the student. Just as important as the knowledge of the action of a muscle is the knowledge of its opponent, and the opponent should be specifically mentioned. The fact that the student when learning the action of a muscle learns that of the opponent will have an important influence on his treatment, for example, of muscular weakness, or paralysis, or of joint injuries. In the case of weakness of any given muscle he will recognize that there can be no recovery if the opposing muscle be allowed to contract, and will immediately guard against such an occurrence. The author believes also that some appreciation of the comparative anatomy of the muscle

is essential for the clinician. He emphasizes the important fact, unfortunately lost sight of by the ordinary clinician, that the one true test of muscle function is the volitional test scientifically applied. As far as methods of treatment are concerned, the principle cannot be repeated too often that an ounce of scientifically directed volitional effort is worth pounds of passive treatment in the form of massage or electrical treatment. This book will be of the greatest value to all interested in orthopedics and physical therapy, and a thorough knowledge of myology is essential to the orthopedic surgeon. Many of the general principles herein outlined are important to the general practitioner as well. The book is well illustrated with practical illustrations.

*Clinical Features of Heart Disease. An Interpretation of the Mechanics of Diagnosis for Practitioners.* By LEROY CRUMMER, M.D., Emeritus Professor of Medicine, University of Nebraska. Introduction by Emannuel Libman, M.D., Professor of Clinical Medicine, Columbia University. Second Edition, Revised and Enlarged. 415 pages. Paul B. Hoeber, Inc., New York, 1930. Price in cloth, \$4.00.

In presenting this second edition there has been no change in viewpoint. Practically every chapter contains some added material. Chapters on acute Rheumatic Fever and Subacute Bacterial Endocarditis have been added. Heart disease is usually progressive. Usually many years elapse between the beginning and end of most cardiac affections, and during this long period much can be done to direct the course of the disease by the well-trained physician. The natural history of heart conditions can be followed more accurately in private than in hospital practice. But a proper foundation is necessary for the recognition and interpretation of clinical phenomena; and this foundation must be a broad one, embracing not only the older methods of physical examination, but also the newer mechanical aids in diagnosis. This volume emphasizes the importance of the simple methods of physical examination, and for this reason, is especially timely as showing that the study of clinical phenomena is as important and nec-

essary now in the training of the physician as it ever was. The volume contains much of value in original observations and suggestions. It is a book of value to the medical student and practitioner alike.

*Nervous Indigestion*. By WALTER C. ALVAREZ, M.D., Associate Professor of Medicine, University of Minnesota (Mayo Foundation). 297 pages. Paul B. Hoeber, Inc., 1930. Price in cloth, \$3.75.

This is a very common-sense treatment of the subject of functional or so-called "nervous indigestion." More than half of the patients who go to a physician for advice in regard to chronic indigestion have symptoms apparently largely "functional" in nature. No organic lesions can be demonstrated in them, and no definite anatomic diagnosis can be made. Because of the difficulty in making a diagnosis, these patients are for the greater part neglected. What clinician and what practitioner concerns himself with the effect of emotion upon the digestive tract? Neither the internist, the neurologist, nor the psychiatrist! Teachers of medicine are interested in the demonstrable lesion, and not in cases in which lesions cannot be found and in which a definite diagnosis cannot be made. Consequently the student is not prepared for the actualities of medical practice, particularly with the problems and difficulties involved in the treatment of the so-called "nervous" patient. That this field is a neglected one in the medical schools is evident to anyone who attends the lectures or clinics, or makes ward rounds. As a consequence it is a far

cry from the medical practice of our teaching clinics to the private practice of a down-town office. In the latter place the young practitioner will learn that in the actual practice of medicine there are many things more important than the giving of drugs or the exploratory operation. The seven chapters in this book are headed: Ways in Which Emotion Can Affect the Digestive Tract, Types of Indigestion, Hints in Regard to the Taking of a History, The Handling of the Nervous Patient, The Treatment of Nervous Indigestion, Some Practical Points About the Physiology and Innervation of the Digestive Tract, and Suggestions for Further Reading. Bibliography and Index follow. The material is presented in a semi-popular style, suitable for reading by the laity, for whom it is apparently intended as much as for the practitioner. And it is worth their perusal. In Chapter Two on Types of Indigestion many grains of pure gold are to be found. This chapter should be read by all those who have "indigestion," and who have an interest in "diets" or "dieting." How certain Sanitarium authorities must gnash their teeth when they read it! The reviewer, as a pathologist, finds himself strangely in agreement with a gastro-enterologist for the first time. This book is important because of the truths it tells. The style is vivacious. The chapters are interleaved with pages of fact and interesting quotations from a great variety of sources. They add a literary flavor to the exposition of sound sense contained in this book.

## College News Notes

### FIFTEENTH ANNUAL CLINICAL SESSION

of the  
AMERICAN COLLEGE OF  
PHYSICIANS  
at BALTIMORE

MARCH 23-27, 1931

Dr. Sydney R. Miller, President, and Dr. Maurice C. Pincoffs, General Chairman, will shortly announce the preliminary program for the Fifteenth Annual Clinical Session of the American College of Physicians at Baltimore, Maryland, March 23-27, 1931. Mr. E. R. Loveland, Executive Secretary, has completed the plans for the exhibits, hotel headquarters, general headquarters for the daily sessions, transportation on the reduced fare plan and many other details.

The Lord Baltimore Hotel, the newest and largest in Baltimore, will be the hotel headquarters. Due to inadequate sized meeting rooms at any hotel, the President, General Chairman and Executive Secretary selected the Alcazar at Cathedral and Madison Streets, for the general headquarters. The Alcazar is operated more or less as a club hotel, but has the largest and most attractive assembly room in the City of Baltimore. Here will be held the registration, the general scientific sessions, the exhibits, etc. The headquarters and offices of the Officers, Regents and members of the Board of Governors will also be located here. The Alcazar operates an attractive dining room where members will be able to secure meals before and after the daily sessions. The Alcazar also has available a few hundred rooms for members of the College who do not desire to take rooms at the Lord Baltimore Hotel.

The time of the Session, March 23-27, and the favorable climate of Baltimore, should induce a much larger attendance than the mid-winter session held during the past year. There will be a large class of new

Fellows and Associates to be taken into the College. It is most important that proposals for membership be filed in the Executive Secretary's office fully a month in advance of the Session.

Members of the College should consider it an obligation to attend the Clinical Sessions, whenever possible. Especially, the attendance and contributions of those so fortunately placed that their opportunities are exceptional means much to the rank and file of physicians who come to these meetings. These annual sessions, held at important medical centers, should always attract large numbers of members, for they furnish a unique opportunity to those who participate in the programs to present the results of their work before an audience competent to appreciate the value of their contributions. As usual, the Baltimore Session will be given to half day clinics, consisting of hospital visits, demonstrations and clinics by the local profession, as well as invited guests, half day general sessions consisting of reports or addresses on medical work by members of the College from other localities, and evening sessions consisting of formal addresses by distinguished guests, American or foreign, and by the President and other representatives of the College. The general sessions, giving an opportunity to members of the College, wherever they may be located, to present the results of their work to a large assembly of men interested in Clinical Medicine, is probably the most important function of the College. There is no substitute for attendance at these important national meetings, for one benefits most through personal contacts and actual presence.

Physicians not already on the mailing list of the College, may receive the program for the Session by application to the Executive Secretary, Mr. E. R. Loveland, 133-135 South 36th Street, Philadelphia, Pa.



## PROMINENT MEMBERS HONORED by UNIVERSITY OF PENNSYLVANIA

On October 10 and 11, the University of Pennsylvania conducted a celebration of medical progress at that institution from its founding to the present time

Dr Alfred Stengel (Master), Ex-President of the American College of Physicians, Professor of Medicine at the University of Pennsylvania School of Medicine and a member of the Board of Trustees of the University of Pennsylvania, was honored with the degree of Doctor of Laws

Dr William Gerry Morgan (Fellow), President of the American Medical Association and an alumnus of the University of Pennsylvania School of Medicine, was honored with the degree also of Doctor of Laws

Surgeon-General Hugh S Cumming (Fellow) of the U S Public Health Service, President of the American Public Health Association, was honored with the degree of Doctor of Science

Among others honored by degrees were Sir Walter Morley Fletcher, Secretary of the Research Council of Great Britain Prof A V Hill, Institute of Physiology, University College, London Prof William H Welch of Johns Hopkins University School of Medicine Dr J Ramsay Hunt, Clinical Professor of Neurology, Columbia University Dr Alonzo Engelbert Taylor, a Director of the Food Research Institute of Leland Stanford University

The Convocation for the conferring of the special degrees was held on October 10, followed by a luncheon, an afternoon session and an evening dinner Dr O H Perry Pepper (Fellow) and Dr William Gerry Morgan (Fellow) were among the dinner speakers

On the Committee of Arrangements appeared the names of the following Fellows of the College

Dr O H Perry Pepper, Vice-Chairman  
Dr George Morris Piersol  
Dr Alfred Stengel  
Dr T Grier Miller

There were clinical presentations, exhibits and demonstrations held at the University Hospital, the Medical Laboratories, the Henry Phipps Institute, the Graduate Hospital, and at other University institutions Dr Stengel and Dr Pepper gave a medical clinic, Dr T Grier Miller gave a gastrointestinal clinic, Dr Russell Richardson (Fellow) gave a clinic on diabetes, Dr E B Krumbhaar (Fellow) gave a demonstration in the Laboratory of Pathology, Dr H R M Landis (Fellow) presented exhibits and demonstrations at the Henry Phipps Institute

Dr O A Fiedler (Fellow), Cardiologist at the Sheboygan Clinic, was chosen President-Elect of the Wisconsin State Medical Society at its recent anniversary meeting in Milwaukee

Acknowledgement is made of the following gifts of publications to the College Library of publications by members

Dr Aaron E Parsonnet (Fellow), Newark, N J, and Dr Albert S Hyman (Fellow), New York, N Y

3 Reprints—"Barium Chlorid in the Stokes-Adams Syndrome of Complete Heart Block"  
"Bundle Branch Block"  
"Myocardosis"

Dr E R Stitt (Fellow), Rear Admiral, U S Navy, is now stationed at the U S Naval Hospital, San Diego, Calif Dr Stitt was formerly Surgeon-General of the Medical Corps of the U S Navy

At the recent British Medical Association's meeting in Winnipeg the following Fellows of the American College of Physicians participated in the program

Dr William Gerry Morgan, Washington, D C

Dr Francis M Pottenger, Monrovia, Calif

Dr A W White, Oklahoma City, Okla  
Dr Lea A Riely, Oklahoma City, Okla

Dr John I Marker (Fellow), Davenport, Ia, addressed the Jackson County (Iowa)

Medical Society on Insurance Examinations, September 17.

Dr L. T. LeWald (Fellow), Professor of Roentgenology, New York University, read a paper entitled "Pulmonary Tuberculosis: Errors in Differential Diagnosis," at the annual meeting of the American Roentgen Ray Society at West Baden, Ind, September 24, 1930

Among biographies with full page portraits appearing in the last edition of the National Cyclopedia of American Biography, appears that of Dr Lorena B Breed (Fellow), Pasadena, Calif

Dr Ralph Pemberton (Fellow), Philadelphia, addressed the Northwest Ohio Medical Society on arthritis at Toledo on October 7, 1930

Dr Ellen C Potter (Fellow), Director of Medicine of the Department of Institutions and Agencies of New Jersey, has been elected a member of the Executive Committee of the National Conference of Social Work, headquarters, Columbus, Ohio

Dr Jacob Gutman (Fellow), Brooklyn, has recently returned from St Louis, where he delivered an address on "Physical Therapy in Cardiac Disease" before the medical section of the American Congress of Physical Therapy

Dr Douglas Brown (Fellow) has been officially transferred from the U S Veterans Hospital at Washington, D C, to the U S Veterans Hospital at Rutland Heights, Mass

Dr Samuel S Riven (Associate) has transferred from the Department of Internal Medicine of the University of Michigan to Vanderbilt Hospital, Nashville, Tenn

Dr Harold Swanberg (Fellow), Quincy, Ill, read a paper on "Uterine Cervical Cancer, Radium Versus Surgery" before the annual meeting of the American Congress of Physical Therapy in St Louis, September 8

Dr E V Goltz (Fellow), St Paul, is the author of an article entitled "Primary Carcinoma of the Lungs and Bronchi" in the September Issue of Minnesota Medicine

Dr James K Hall (Fellow), Richmond, Va, has been appointed a member and Chairman of the Committee on Ethics and Judiciary of the Medical Society of Virginia to fill the vacancy caused by the death of Dr Garnett Nelson (Fellow), of Richmond

Dr O H Perry Pepper (Fellow), Philadelphia, is the author of an article, "Tardy Symptoms of Congenital Lesions," appearing in the September Issue of the Virginia Medical Monthly

Dr Philip S Smith (Fellow), Abingdon, Va, has an article in the same issue, entitled, "Symptomatology of Hypothyroidism"

Dr Roscoe H Beeson (Fellow), Muncie, Ind, Dr J A Barger (Fellow), Rochester, Minn, and Dr James B Herrick (Fellow), Chicago, Ill, spoke on "State Medicine," "Diseases of the Colon," and "Importance of the History and Physical Examination in Diagnosis," respectively, at the 81st annual session of the Indiana State Medical Association at Fort Wayne, September 24-26

At the 56th annual meeting of the Oregon State Medical Society at Portland, September 18-20, Dr Noble Wiley Jones (Fellow), with Dr Samuel J Newsom, delivered a paper on "Experimental Focal Infection in Relation to Cardiac Pathology", Dr Frank R Menne (Fellow) and Dr Marr Bisailon (Fellow), with Dr Thomas Robertson, delivered a paper on "Primary Bronchogenic Carcinoma, a Clinical and Pathologic Study"

Dr Paul H Ringer (Fellow), Asheville, N C, and Dr Horton R Casparis (Fellow), Nashville, Tenn, conducted a course of clinics at the South Carolina State Park Sanatorium, July 30-31, under the auspices of the South Carolina Tuberculosis Association and the State Board of Health, for South Carolina physicians

Surgeon-General Hugh S Cumming (Fellow), U S Public Health Service, addressed the American Catholic Hospital Association of the United States and Canada at Washington, September 2-5, on the subject, "The Hospital as a Factor in Public Health"

Dr Oliver P Kimball (Fellow), Cleveland, Ohio, received honorable mention for his essay dealing with the goiter problem, as submitted to the American Association for the Study of Goiter at their Seattle meeting some weeks ago

Dr Peter M Murray (Fellow), New York, N Y, was elected President-Elect of the National Medical Association at its 35th annual session at Indianapolis, during late August

Dr David Marine (Fellow), New York, N Y, addressed the American Chemical Society's meeting at Cincinnati, September 8-12, on "The Possible Nature of the Goiter-Preventing Agent in Plants"

Dr Nathan S Davis, III (Fellow), Chicago, addressed the Rock Island County Medical Society, September 9, on "Diagnosis and Treatment of Heart Disease"

The Northern Minnesota Medical Association held its annual meeting, September 19-20, at Moorhead, Minn. Among Fellows of the College on the program for stated addresses were

Dr Walter C Alvarez, Rochester—"Methods of Diagnosing Gastro-Intestinal Disease from a Careful History of the Symptoms",

Dr Henry W F Woltman, Rochester—(Subject not announced)

The Clinical Committee of the Medical Society of the County of Kings each year offers a fall series of practical lectures. A number of the Fellows of the American College of Physicians appear on their programs

October 10

Dr George I Swetlow, Brooklyn—"Pain Its Diagnostic Significance

Its Treatment by Alcohol Nerve Block",

October 17

Dr Walter C Alvarez, Rochester—"Physiologic Knowledge Applied to Treatment of Gastro-Intestinal Diseases",

October 31

Dr C Saul Danzer, Brooklyn—"Arteriosclerosis Some Phases of the Newer Knowledge Applicable in General Practice"

November 7

Dr Murray B Gordon, Brooklyn—"Endocrine Diseases and Disorders in Children",

November 14

Dr Robert A Cooke, New York City—"Allergic Conditions Encountered in General Practice",

November 28

Dr John A Lichty, Clifton Springs—"Diarrhea"

Dr W McKim Marriott (Fellow), St Louis, gave the following series of post-graduate lectures under the auspices of the Academy of Medicine of Lima and Allen County, Ohio

September 15 "Practical Points in Care and Feeding of Infants" and "Recent Investigations on Nature and Treatment of Nephritis",

September 16 "The Clinical Application of Recent Studies Concerning Chemical Equilibrium in the Body" and "The Application of Specific Measures in the Prophylaxis and Treatment of Infectious Diseases"

Under the presidency of Surgeon-General M W Ireland (Fellow), Washington, D C, the American College of Surgeons held its 20th annual clinical congress in Philadelphia, October 13-17, with headquarters at the Bellevue-Stratford Hotel

Dr Thomas C McCleave (Fellow), Berkeley, Calif, addressed the Alameda County (Calif) Medical Society, September 15, on "Bacteriophage Treatment of Typhoid"

Dr Wardner D Ayer (Fellow), Syracuse, used as his subject "Neurological Aspect of the Fractured Skull" in an address before the Sixth District Branch of the Medical Society of the State of New York at Cooperstown, September 23

Dr Elliott P Joslin (Fellow), Boston, was guest speaker at the opening of a diabetic camp on the estate of Dr Henry J John (Fellow) in Geauga County (Ohio), during the summer

Dr Carl J Wiggers (Fellow), Cleveland, represented Western Reserve University at the medical meetings in Brussels held during the summer, celebrating the one hundredth anniversary of Belgian independence

Dr Christopher G Parnall (Fellow), Rochester, N Y, presided at the 32nd annual convention of the American Hospital Association at New Orleans, October 20-24. Among the speakers were Dr Ernest S Mariette (Fellow), Oak Terrace, Minn, his subject being, "The Sanatorium, Past, Present and Future"

Among speakers and their addresses at the 41st annual meeting of the Association of American Medical Colleges, held at the University of Colorado School of Medicine, Denver, October 14-16, were the following Fellows

Dr Harold E Robertson, University of Minnesota Graduate School of Medicine

—"Development of the Liaison Activities of a Department of Pathology",

Dr Charles C Bass, Tulane University of Louisiana School of Medicine—"New Teaching Clinic and Curriculum at Tulane",

Dr Torald H Sollmann, Western Reserve University School of Medicine—"Report of Committee on Aptitude Test",

Dr Walter A Bloedorn, George Washington University School of Medicine—"Relation of Autopsies to Teaching"

Dr A S Warthin (Master) delivered three addresses before the Utah State Medical Association at the Meeting in Salt Lake City, September 9-12

Dr B S Pollak (Fellow), Medical Director of the Hudson County Tuberculosis Hospital and Sanatorium, Secaucus, N J, returned about September first from Oslo, Norway, where he was a delegate to the International Union Against Tuberculosis. Dr Pollak was also a delegate to the Second Congress at Stockholm

Dr Grafton Tyler Brown (Fellow), Washington, D C, has been re-elected Chairman of the Membership Committee of the Medical Society of the District of Columbia

Dr C O Bailey (Fellow), Dallas, Texas, read a paper on "Carcinoma of the Cervix Uteri With Treatment" before the Texas State Medical Association in annual session at Mineral Wells, May 7

Dr Roger M Choisser (Fellow), Washington, D C, Lieutenant Commander, Medical Corps, U S Navy, and Director of Laboratories, U S Naval Medical School, read a paper before the Fairfax County Medical Society of Virginia, August 7, on the "Recent Advances in Medical Diagnosis by Means of Laboratory Procedures"

Dr Joseph Doane (Fellow), Philadelphia, is scheduled to address the American College of Surgeons and the Pennsylvania State Medical Association at their annual meetings in October. Dr Doane is Associate Professor of Medicine in the Graduate School of Medicine of the University of Pennsylvania, and Associate Professor of Medicine in the Temple University School of Medicine

Dr William D Reid (Fellow), Assistant Professor of Cardiology at the Boston University School of Medicine, has published the following papers since January 1, 1930

"The Prognosis of Heart Diseases in Pregnancy"—American Journal of Obstetrics and Gynecology, January, 1930

"The Treatment of Neurosis (Cardiac)"—New England Journal of Medicine, February 6, 1930

"Spinal Deformity as Cause of Cardiac Hypertrophy"—The Journal of the

American Medical Association, February 15, 1930

"Wenckebach Angina Pectoris (translation)"—Medical Journal and Record, February 19 and March 5, 1930

"The Differential Diagnosis of Cardio-vascular Syphilis"—The American Journal of Syphilis, April, 1930

"Permanent Bradycardia Following Diphtheria, Case Report"—American Heart Journal, April, 1930

At the annual meeting of the American Heart Association at Detroit, June 24, he delivered an address on "The Diagnosis of Cardiovascular Syphilis"

Under the auspices of the Gorgas Memorial Institute, an article entitled "Trench Mouth", by Dr Oliver T Osborne (Fellow), Emeritus Professor of Therapeutics, Yale School of Medicine, was syndicated in a large number of daily papers on July 15

Lieutenant Colonel Reynold Webb Wilcox, M D, D C L (Fellow) and Ex-President), is recovering from a severe illness of July at his country place in Madison, Conn. He will shortly return to his home at 90 Bayard Lane, Princeton, N J, where he will be glad to see his friends

Dr Louis A Milkman (Associate), Scranton, Pa, delivered a paper before the Pennsylvania Roentgen Ray Society at Huntington, Pa, May 14, 1930, on "Bone Lesions as seen by the Roentgenologist"

Dr Milkman is the author also of a paper on "Pseudofractures (Hunger Osteopathy, Late Rickets, Osteomalacia)" in the July Issue of the American Journal of Roentgenology and Radium Therapy

Dr Carl V Vischer (Fellow), Philadelphia, is the author of a case report, "Multiple Sarcomata", which appeared in the August Number of the Hahnemannian Monthly

Dr T E Rogers (Fellow), Macon, Ga, discussed clinical cases at the Macon Medical Society's meeting on July 2

Dr Henry Green (Associate), Dothan, Ala, was elected a member of the Council of the Chattahoochee Valley Medical and Surgical Association, July 9

Dr Edson W Glidden (Fellow), former Superintendent of the Georgia State Tuberculosis Sanatorium at Alto, has accepted an appointment as Superintendent and Medical Director of the Worcester County Sanatorium at Worcester, Mass

Practically all of the Officers of the American Therapeutic Society for 1930-31 are members of the American College of Physicians, as follows

President, Clement R Jones (Fellow), 1st Vice President, William J Mallory (Fellow), 2nd Vice President, William Engelbach (Fellow), 3rd Vice President, Leonard Murray (Fellow), Secretary, Grafton Tyler Brown (Fellow), Treasurer, Truman G Schnabel (Fellow)

#### COUNCIL

Chairman, Noble P Barnes (Fellow), Secretary, Grafton Tyler Brown (Fellow), Oscar W Bethea (Fellow), Harlow Brooks (Fellow), Truman G Schnabel (Fellow), Harvey G Beck (Fellow), Charles G Jennings (Master), William Fitch Cheney (Fellow), E Bosworth McCready (Fellow), Frank Smithies (Master), Francis M Pottinger (Fellow), Editor, Alpheus F Jennings (Fellow)

#### GIFTS TO THE COLLEGE LIBRARY

The following donations of reprints have been acknowledged, indexed and duly added to the College Library of publications by members

Dr Frederic J Farnell (Fellow), Providence, R I

One Reprint—"The Individual Criminal and His Cure"

Dr Alvis E Greer (Fellow), Houston, Texas

Three reprints—"The Physician of Yesterday and Tomorrow", "Pulmonary Syphilis", "Dental Infections and Systemic Disease"

Dr Louis A Milkman (Associate), Scranton, Pa

One Reprint—"Pseudofractures (Hunger Osteopathy, Late Rickets, Osteomalacia)"

Dr H Brooker Mills (Fellow), Philadelphia, Pa

Two Reprints—"Infant Feeding", "Pyloric Obstruction"

Dr Carl V Vischer (Fellow), Philadelphia, Pa

One Reprint "Multiple Sarcomata"

There are a number of books, of which Fellows of the College are authors, that have not yet been donated to the College Library. Fellows are urged especially to donate copies of their books to this Library, which will become a memorial to the College members

Dr E Roland Snader, Jr (Fellow), Philadelphia, Assistant Physician to the Hahnemann Hospital, held a clinic in Physical Diagnosis before the students on May 1. The report of the clinic, "Congestive Heart Failure", was published in a recent issue of the Hahnemannian Monthly

Dr Cyrus W Strickler (Fellow), Atlanta, delivered a paper on "The Pneumonias" at the Tenth District Medical Society's meeting at Louisville, August 28

Dr T F Abercrombie (Fellow), Atlanta, Commissioner of Health, attended the conference on Malaria at Sandersville, Ga, August 6, said conference having been arranged by the Washington County Medical Society in co-operation with several other organizations

Dr William R Dancy (Fellow), Savannah, Ga, was elected First Vice Commander-in-Chief of the Sons of Confederate Veterans at their recent reunion at Biloxi, Miss

Dr Thomas B Fitcher, Baltimore, has been elected President of the Association of American Physicians

Dr Wilburt C Davison (Fellow), formerly Assistant Dean of Johns Hopkins University Medical School, Baltimore, now

Dean of the Duke University Medical School, heads the staff of the new \$1,000,000 hospital and medical school, which was opened in July. The hospital has a capacity of four hundred beds, the largest general hospital in the Carolinas. The medical school, which opened October 1, has a maximum capacity for three hundred students

Dr William deB MacNider (Fellow), Chapel Hill, N C, has been elected as Examiner in Pharmacology on the National Board of Medical Examiners

Dr Albert H Hoge (Fellow), Bluefield, W Va, has been appointed by the Governor of that state as a member of the West Virginia Public Health Council

Dr Otis B Nesbit (Fellow), Gary, Ind, recently resigned as a member of the Board of Managers of the Lake County Tuberculosis Hospital

Dr G Harlan Wells (Fellow), Philadelphia, delivered the Endowment Lecture before the American Institute of Homeopathy at Montreal, Canada, on June 26, 1930. The Lecture, "Homeopathy and the newer Concept of Cellular Therapy", was published in the August, 1930, Issue of the Journal of the American Institute of Homeopathy

Dr Ross V Patterson (Fellow), Dean of Jefferson Medical College of Philadelphia, was installed at President of the Pennsylvania State Medical Association at its Johnstown meeting, October 7

The following Fellows of the College contributed papers

Dr Joseph T Beardwood, Jr, Philadelphia (With Frederick A Bothe, Philadelphia) "Surgery and Diabetes"

Dr Joseph C Doane, Philadelphia "Is the Inauguration of the Teaching of Clinical Medicine in a General Hospital Possible?"

Dr T Grier Miller, Philadelphia "The Precursors of Cancer of the Stomach"

Dr Henry R M Landis, Philadelphia  
(With Jacob W Cutler, Philadelphia)  
"The Medical Aspects of Renal Tuberculosis"

Dr Francis J Dever, Bethlehem "Symptomless, Extensive Carcinoma in the Abdominal Cavity with Fatal Hemorrhage"

Dr Stanley D Conklin, Sayre, Pa  
"Acute Pneumococcic Peritonitis with Acute Empyema—Left, Metastatic"

Dr Walter M Bortz, Greensburg, Pa  
"Hepatomegaly"

Dr Jesse L Lenker, Harrisburg "Pericarditis Calculosa"

Dr Roy R Snowden, Pittsburgh "The Diagnosis of Hyperthyroidism"

Dr Emanuel Libman, New York City (Guest) "Clinical Studies on Pain in Medical and Surgical Conditions"

Dr Horace B Anderson, Johnstown  
"Diagnosis of Early Circulatory Insufficiency"

Dr George W Grier, Pittsburgh  
"Roentgen Diagnosis of Empyema"

Dr Harold W Jones, Philadelphia  
"Practical Points Concerning Blood Transfusion"

Dr Alvin E Siegel, Philadelphia "Is There an Ideal Infant Food?"

Dr Harvey O Rohrbach (Associate), Bethlehem, gave a paper on "Proper Use of Insulin and Diet in Juvenile Diabetes"

Dr William J Kerr (Fellow), San Francisco, is Chairman of the San Francisco Heart Committee, which was recently organized by a group of one hundred members of the San Francisco County Medical Society to amalgamate all interests in the City concerning problems of heart disease

Dr Fred M Smith (Fellow), Iowa City, addressed the Iowa State Dietetic Association at its annual meeting, July 18-19, on "The Irritable Colon"

Dr Isaac I Lemann (Fellow), New Orleans, addressed the Orleans Parish Medical Society, recently, on "Meningococcemia for Eight Months Following Meningitis Recovery"

Drs Clifford J Barborka (Fellow), Rochester, Minn, and Rodney W Bliss (Fellow), Omaha, Nebr, addressed the Elkhorn Valley Medical Society of Nebraska, July 29, on obesity and on the heart, respectively

Dr Henry D Jump (Associate), Philadelphia, addressed the Cumberland County (New Jersey) Medical Society, July 8, on quinidin in heart disease

Dr James J McGuire (Fellow), Trenton, N J, was elected Secretary of the New Jersey State Board of Medical Examiners on July 10

Dr David Riesman (Fellow), Philadelphia, delivered the oration in medicine entitled, "Hypertension and Longevity", at the 89th annual meeting of the Wisconsin State Medical Society at Milwaukee, September 10-12

Dr Frederick C Rinker (Fellow), Norfolk, Va, was made President of the newly formed Second District Medical Society at Suffolk, Va, recently

Dr Casper H Benson (Fellow), Columbus, Ohio, was the chief speaker at the joint meeting of the Preston and Monongahelia County Medical Societies (West Virginia), held at the State Tuberculosis Sanatorium, Hopemont, July 15 Dr Benson's subject was "Early Diagnosis of Pulmonary Tuberculosis"

The Children's Free Hospital of Louisville has become affiliated with the School of Medicine of the University of Louisville Dr Philip F Barbour (Fellow) is Chief of Staff of the Hospital, and Dr John Walker Moore (Fellow), Dean of the Medical School, is a member of the Executive Committee, ex officio

Dr Walter E Vest (Fellow), Huntington, used as his title, "The Importance of Attendance at Medical Meetings" in a talk delivered at the third quarterly meeting of the Central West Virginia Medical Society, July 16

## OBITUARY

Dr Isidor Betz (Associate), Brooklyn, N Y, died July 13, 1930, of gall stones, aged 45 years

Dr Betz graduated from the Long Island College Hospital in 1910. He did postgraduate work during 1927 at the University of Vienna. He was a member of the North Brooklyn Medical Association, the Williamsburgh Medical Society, the New York State Medical Association and the American Medical Association. He was an Associate of the American College of Physicians by virtue of his membership in the American Congress on Internal Medicine, before the merger of the Congress with the College.

Dr Betz was consultant at the Menorah Home for Aged and a member of the staffs of Greenpoint, Beth Moses and St Catherine's Hospitals.



# Studies on the Etiology of Goiter Including Graves' Disease.\*

By DAVID MARINE, *New York*

IT is scarcely necessary to repeat to this audience the usual expression of feeling greatly honored at being invited to discuss certain features of my work in the University where I spent 15 pleasant years and where foundations of anything I have done in medicine were laid. It is necessary, however, out of fairness, to explain to this audience that much of the work I shall talk about tonight is the combined outcome of the friendly discussions, criticisms and hard work of men well honored and now living in Cleveland. I have particularly in mind the names of Lenhart, Stewart, Sollmann, Crile, Graham and Kimball.

Special interest in the problem of goiter was aroused the morning I arrived in Cleveland to join the resident staff of Lakeside Hospital. While walking from the Hollenden Hotel to the hospital, I saw several dogs with enlarged necks, three of which I stopped and examined. Since then my spare time has been spent working on one or another subject directly or indirectly connected with the goiter problem.

My curiosity was only that natural to a young medical graduate who had been suddenly transported from a region (Baltimore) where goiter was rare to a district where it was endemic. I quickly learned that my curiosity had been shared by other and more able medical men for the past 3000 years and that much of the knowledge which has now been established by painstaking investigation was suspected or known in a general way by the ancients.

The term goiter as now used is restricted to enlargement of the thyroid gland and is believed to have been derived from the Latin *guttur*, meaning throat. The first complete anatomical description of this gland was given by Thomas Wharton, the English anatomist, and published in 1659. He also gave it its present name. Every school child has a general idea of the size, location and outline of the thyroid sufficient to meet all practical needs and for our present purposes it is not necessary to review the anatomy in detail.

On the other hand, a general idea of the function of this important gland is absolutely essential for an understanding of the diseases with which it is more or less intimately associated. The

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\*McBride Lecture, Western Reserve University, delivered Nov. 11, 1929.

story of our present knowledge of thyroid function may be more impressively told in the form of a historical summary of the more outstanding facts

Prior to 1874 some of the functions ascribed to the thyroid, that is, that it served to protect the vocal cords from cold, that it produced a secretion to moisten the larynx, that it gave form to the neck, that it served as a vascular shunt to control the brain circulation, were highly fanciful. In 1874 Sir William Gull published an account of a peculiar cachexia associated with atrophy of the thyroid. The outstanding clinical manifestations of this cachexia were loss of hair, drying of the skin, hard edematous thickening of the subcutaneous tissues, marked mental deterioration, extreme sensitiveness to cold and very great lessening of all bodily functions. Because of the peculiar changes in the skin and subcutaneous tissues, Sir William Ord in 1878 gave it the name "myxedema." The observation of Gull, therefore, marks the beginning of our real knowledge of thyroid physiology.

In 1882 the Reverdin brothers published a brief report and in 1883 Theodore Kocher published a much more complete account of the effects of complete removal of large goiters in human beings.

Most of the patients upon whom this operation was performed developed what we now recognize as parathyroid tetany but a few developed a symptom-complex (cachexia strumaprima) which Kocher recognized as being essentially identical with that described by Gull nine years earlier. This condition was soon produced at will in

many species of animals by the removal of the thyroid.

In 1891 Murray reported the cure of a case of Gull's disease by injecting a glycerol extract of fresh sheep's thyroid and about the same time in Germany it was observed that feeding the gland by mouth, either fresh or dried, produced the same effect.

In 1895 Magnus-Levy, using the newly developed calorimeter, found that the essential effect of feeding thyroid gland substance either to individuals with myxedema or to normal persons was to raise their total metabolism, that is, it greatly increased their oxygen consumption and heat production and up to the present time this acceleration of oxidation processes is the only known physiological and pharmacological effect of the thyroid.

Also in 1895 Baumann of Freiburg discovered the presence of iodine as a normal constituent of the gland and Oswald of Zurich in 1899 showed that the iodine was contained mainly in the colloid material and firmly bound with the globulin fraction as an iodothyroglobulin.

The work done in this university between 1905 and 1910 by Williams, Lenhart and myself showed that the iodine store was intimately related to the structure and the function of the thyroid gland. It was demonstrated that the essential change in the development of goiter was a tremendous decrease in the iodine store in the gland and that this held true for all the species of animals examined. It was further shown that the administration of iodine caused a very rapid storage of this substance in the gland and brought about the involu-

tion of any existing hyperplasia as well as preventing any possible development of hyperplasia

In 1916 Kendall of the Mayo Clinic reported the isolation of a crystalline substance from the thyroid containing about 65% of iodine which he named thyroxin and which was found to have effects on metabolism similar to those observed by Magnus-Levy in 1895 following the administration of the whole gland substance. Kendall attempted to determine the structure of thyroxin but failed. In 1926 Harrington and Barger in a brilliant research perfected a simple method of isolating the substance in larger amounts, succeeded in determining its chemical structure and in the following year made it synthetically.

Whether thyroxin is the only active principle of the thyroid is not known, but it certainly accounts for its chief and only known function. To summarize: The major function of the thyroid is to provide the means through its iodine containing hormone, thyroxin, for maintaining a higher rate of metabolism or oxidation processes than would otherwise exist and also through fluctuations in activity it provides a means for varying the rate of metabolism to meet changing physiological needs.

Another important phase of thyroid function deals with its interrelations with other glands, as for example, the pituitary gland, the suprarenals, the ovaries, the testes and thymus. Our knowledge of these interrelations is still very meagre and a general summary would not be very helpful here. However, certain of these interrela-

tions will be briefly referred to in the discussion of thyroid diseases.

The important diseases of the thyroid associated with disturbances of its functions may be divided into two general groups as follows:

Group I. Thyroid insufficiencies (hypothyroidism)

- 1 Simple or endemic goiter
- 2 Myxedema
  - a of infants (cretinism)
  - b of adults (Gull's disease)

Group II. Graves' disease (hyperthyroidism)

As I shall say only a few words regarding Graves' disease, it will be better to dispose of this before going on with the main topic of this lecture.

Graves' disease is a serious disease, easily recognizable and characterized by a chronic afebrile increase in metabolism and heart rate, marked general weakness, a highly nervous state and less frequently by protrusion of the eyes and thyroid enlargement. The incidence is rapidly increasing in all industrialized countries and concerning its nature very little that is definite is known. The view that it is essentially a thyroid disease is still the prevailing one but I am convinced that the primary and fundamental disturbance lies elsewhere—probably in a deficiency of some function of the suprarenal cortex and sex glands, which has to do with the regulatory control of oxidation processes in the various tissues. Graves' disease is clearly a loss of control of these oxidation processes and as a result of this there is an excessive

production by the thyroid of its very powerful activator of oxidation, thyroxin.

Three facts of importance have been discovered during the last ten years bearing directly on the etiology. The first is that a symptom complex closely resembling Graves' disease can be produced in a large percentage of rabbits and cats by sufficient injury of the suprarenal glands. The outstanding symptoms of Graves' disease which can thus be produced experimentally are increased metabolism, myasthenia, regeneration of the thymus and lymph glands, increased appetite, a change in temperament, increased irritability and hypersusceptibility to drugs. The conclusion that the symptom-complex which follows sufficient injury of the suprarenals is closely related to Graves' disease is not generally accepted but it cannot be ignored even though it is only a very crude reproduction, or glimpse of the natural disease. One obvious reason for this crudeness is that the suprarenal gland is at least a dual gland whose functions are to some extent antagonistic and in injuring the cortical portion we of necessity seriously cripple the medulla, or epinephrine secreting tissue, while in Graves' disease this is not the case. As is well known, epinephrine is the most rapid activator of metabolism known.

The second fact deals with the attempts to obtain a physiologically active substance from the suprarenal cortex that would lower or regulate thyroid activity. A great number of extracts have been studied by various workers, notably Stewart and Rogoff in this university, but I can here men-

tion only those that appear to have a bearing on Graves' disease. During the last ten years we have consistently observed that glycerol extracts of fresh ox suprarenal cortex when fed to cases of Graves' disease regularly caused an outstanding gain in weight, a gain in muscle strength and gradual lowering of the metabolism. Attempts to concentrate this substance always ended in failure. On this account we were never able to obtain more than a glimpse of its activity and the impression that it was unstable in air.

The third fact is the discovery reported last year by Szent-Gyorgyi. He isolated from the suprarenal cortex an active reducing substance in crystalline form, which is unstable and readily destroyed in the presence of atmospheric oxygen and which he thought was a hexuronic acid. The work which we have so far done with this substance would indicate that it has very striking effects on the oxidation and reduction processes going on in the living tissues and particularly that it lowers the activity of the thyroid gland, as indicated by the fact that it causes thyroid involution.

These three facts—first, the experimental production of a Graves' disease-like symptom-complex in animals, second, the slight but obvious beneficial therapeutic effect of cortical extracts administered by mouth to cases of Graves' disease and third, the isolation of a highly unstable hexuronic acid from the cortex which involutes thyroid hyperplasia—I believe mark a definite advance toward the solution of Graves' disease by establishing with certainty that some internal secretion of the suprarenal cortex and sex

glands play an important role in regulating tissue oxidations, particularly when considered in association with the long known fact that the most outstanding physiological abnormality in Graves' disease is a derangement of the regulatory control of tissue oxidations

After this digression we can turn to the main subject of this talk, namely, thyroid insufficiencies of which simple or endemic goiter, cretinism and myxedema are the three outstanding clinical associations. So far as is known, the great medical character of the middle ages, Paracelsus, was the first to point out the close relationship between endemic goiter and cretinism. All subsequent study has strengthened this association and firmly established the view that they are but different stages or degrees of the same nutritional fault. This idea was first forcibly expressed by Morel in his famous dictum, "Goiter is the first step on the road to cretinism", and later by Koestl, that the condition which produced goiter when it is weak also produces cretinism when it is intense.

As endemic cretinism in man does not occur in America I shall limit the discussion to simple or endemic goiter.

#### *Occurrence and Distribution*

Simple goiter includes those thyroid enlargements in man and animals which were formerly grouped under endemic, epidemic, sporadic and physiologic. It may occur in any land and fresh water animal with the ductless thyroid. Animals living in the sea are free from the disease. On the seacoast generally it is ordinarily rare in man and the cases seen are usually in

women and in association with pregnancy and lactation. It occurs in all races, in all climates and at all inhabitable altitudes. In the temperate zones there is a seasonable variation, both in man and animals. It develops more frequently during the late winter and early spring months. Similar seasonal variations also occur in the iodine store of the thyroid as pointed out by Seidell and Fenger. While goiter may occur anywhere, even in mid-ocean, as on one of Capt. Cook's voyages in 1772, one of the most striking characteristics is the increased incidence in certain more or less defined regions of the world, in so-called districts of endemic goiter (Hirsch). The most notable of these districts are the Himalaya Mountain region of South Central Asia, the Alps, Pyrenees and Carpathian Mountain regions in Europe, the Andean plateau of South America. In North America the most important areas are the St. Lawrence River and Great Lakes basin, extending west through Minnesota, the Dakotas and the adjacent Canadian provinces and also the Pacific Northwest, including Oregon, Washington and British Columbia. Less important foci occur throughout the Appalachian Mountain region, the Rocky Mountain states and states in the Great Central Basin. It will be noted that most of these regions are mountainous, although there are numerous exceptions. Of greater importance is the occurrence of endemic goiter for the most part on soils deposited from the last glacial period.

There is also general evidence of variations in the incidence of goiter in these districts during the last 100 years. There are many reports of the

sudden occurrence of large numbers of goiters, the so-called epidemics, both in man and animals. In man these so-called epidemics have for the most part occurred in military garrisons, in institutions and in schools. These outbreaks have usually been in districts where the ordinary incidence of goiter is high and in newly arrived people. I have had opportunity of investigating such outbreaks in dairy herds, on poultry farms and in fish hatcheries. Some of these outbreaks were in goiter regions while others were not, showing that with the optimum conditions for its development present, goiter may occur anywhere.

Beginning about the age of puberty, females are more often affected than males. In the districts of severest endemic goiter this difference in incidence due to sex is masked. In such regions all of the inhabitants may be affected. In non-goiter regions where only sporadic cases occur these are usually seen in women. Striking an average between these two extremes one may say that in general simple goiter is two or three times more common in females. In the lower animals a difference in incidence due to sex has not been demonstrated. The periods in life when simple goiter most frequently develops are (a) during fetal life, (b) during pregnancy and lactation, (c) during puberty and (d) during the menopause.

### *Etiology*

Despite the fact that the cause of endemic goiter has been sought since the earliest days of medicine, the fundamental cause is still unknown. A great variety of agents have been

brought forward from time to time as casual factors.

In 1867 St. Lager grouped the various causal factors under forty headings, most of which now have only a folklore or legendary interest. Certain of them, as for example water, poverty, damp sunless habitations and especially diet, are of general importance today. A great variety of mineral constituents of soil and water, as for example salts of calcium and magnesium, sulphides, particularly of iron, fluorides and silica, were at one time suspected. With the development of bacteriology and protozoology the view that goiter might be due to a specific living virus was widely adopted and is still held by some. Many types of organism, bacteria, fungi and protozoa, have been described. McCarrison thought that a member of the colon group of bacteria was the cause. Chagas thought a trypanosome caused endemic goiter in Brazil and numerous reports have appeared suggesting organisms of the diphtheroid group.

Despite this enormous amount of work nothing suggesting a direct infecting agent has been proven. That bacterial toxins may indirectly stimulate the thyroid to enlargement is well known, as for example pulmonary tuberculosis, syphilis and pneumonia. Water has been associated as a carrier of the goiter producing agent by all peoples from the remotest times. Livingstone reported that the inhabitants of Central Africa held this belief. Barton, in 1800, stated that the Indians inhabiting the shores of Lakes Ontario and Erie thought that water which contained soluble products of decomposing leaves and other vege-

table matter was responsible since goiter was more common in the fall and winter months. The Romans were convinced that snow water was a cause. Water certainly is a factor in the etiology of goiter and the conflicting data in the light of our present knowledge could be best correlated by assuming a deficiency of some substance (iodine) which is necessary for the prevention of goiter rather than that water contains some virus or toxin capable of inducing goiter.

The present view of the cause of simple goiter assumes that it is a work or compensatory hypertrophy of the thyroid depending immediately upon a relative or absolute deficiency of iodine.

This leaves the ultimate or fundamental causes of iodine deficiency still to be determined but concerning which very important contributions have recently been made, to which I shall presently refer.

It is conceivable that the deficiency of iodine may be due to, first, factors which bring about an abnormally low intake of iodine; second, to factors which interfere with the absorption or utilization of an otherwise normal intake, or third, factors which temporarily or periodically increase the needs of the body for thyroxin, that is, factors which create a relative insufficiency of iodine. These three groups may be examined further.

Group 1—Factors bringing about an abnormally low iodine intake. This would partially explain the occurrence of endemic goiter. It is a simple, easily understandable conception and compatible with all the facts so far as it goes, but unfortunately the problem

of goiter is much more complicated. The idea that goiter is due to a low iodine intake is not new. As early as 1830, that is within 19 years of the discovery of iodine as an element, such views were expressed. To be sure, a low chlorine intake was also advanced as the cause but this should have supported instead of detracting from the idea of the iodine deficiency since these two elements are so closely associated in nature.

The work of Chatin published in 1852 deserves special mention. He showed that there was a low iodine content in soil and water in districts of endemic goiter. His results were attacked and unfortunately so discredited on the ground of faulty technique and inadequate methods that further study of this important lead was blocked for 45 years, that is, until Baumann discovered iodine as a normal constituent of the thyroid in 1895. During the past 20 years very extensive analyses of foods, soils and water for iodine, particularly by McGlendon and Remington in this country and by von Fellenberg in Europe, have been made and all confirm Chatin's original claim.

Group 2—We have no information at present in regard to factors which interfere with the absorption or utilization of iodine in the body. It is conceivable that intestinal bacteria or various parasites could utilize or divert the iodine intake or that inherited or acquired defects in metabolism could prevent the thyroid gland from utilizing iodine but the evidence is entirely against any influence by these factors. Indeed, in all the vast experience now available no one has seen anything which suggests that the thy-

roid gland is unable to make thyroxin in a few hours after iodine is administered.

Group 3—Factors which temporarily or periodically increase the need of the organism for thyroxin. This group is more difficult to define or understand and from evidence now available it is by far the most important. There are many factors which are known to temporarily increase the needs of the organism for thyroxin, that is, factors which create a relative iodine insufficiency. Among the more important may be mentioned, *food, pregnancy, infectious diseases, puberty* and *Graves' disease*. As already mentioned, food has long been known to influence the thyroid. St. Lager mentions that the Alpine people thought that eating large quantities of pork fat caused thyroid enlargement. Baumann observed that diets consisting entirely of meat caused a reduction in the iodine store of dogs' thyroids. The work of Lenhart and myself on goiter in brook trout demonstrated that a diet of pigs' liver was the major cause. Our observations in dairy herds showed that extensive feeding of oil cake often led to goiter in cattle.

About two years ago Chesney and Webster in Johns Hopkins University found that rabbits fed mainly with fresh cabbage developed goiter in from two to three months. This observation gave us a cheap, simple and practical method of producing goiter in the most practical of all laboratory animals. Taking up this work with my colleague, Dr. Emil J. Baumann, we quickly found that by steaming the cabbage for thirty minutes, goiter

could be produced in seven to nine days instead of the two or three months required when fresh cabbage was fed. We further found that the cabbage cake from which 60% of its weight had been expressed as press juice was even more potent than the whole cabbage. We further observed that whereas hashed steamed cabbage was as potent as unhashed cabbage, hashed fresh cabbage lost most of its goiter producing quality. From these data we concluded that the goiter producing substance could be destroyed quickly by enzymes although it was heat stable and resisted oxidation in the air. We further observed that there was a very great seasonal or climatic variation in the goiter producing quality of cabbage. So-called summer cabbage was practically inert, whereas cabbage maturing late in the autumn, so-called winter cabbage, was usually extremely potent. All these observations indicated that we were dealing with at least two factors, (1) a goitrogenic and (2) an anti-goitrogenic, both of which show quantitative variations. The discovery last year by Szent-Gyorgyi helped us greatly at this point. As already mentioned, he isolated from cabbage, oranges and suprarenal cortex a very powerful auto-oxidizable substance. We have injected concentrates of this substance into rabbits and found that it was strongly anti-goitrogenic. It was now definite that in cabbage there exists two substances—one, a stable, powerfully goitrogenic substance occurring mainly in winter cabbage and the other, a very unstable, powerfully anti-goitrogenic substance occurring in greatest concentration in summer cab-



bage Iodine is also antigoitrogenic but acts quite differently from the hexuronic acid Iodine prevents goiter by supplying the necessary element from which the thyroid can readily make thyroxin while hexuronic acid appears to act by providing another means of augmenting tissue oxidations and in this way relieving or sparing the thyroid

The goitrogenic substance has not yet been isolated We know that it exists in many other members of the cabbage family and that it shows great seasonal variation As above mentioned, a good cabbage will produce a palpable goiter in the rabbit in seven days The development of the goiter is accompanied by a fall in metabolism, as shown by Webster and Chesney, which may be as rapid and as marked as that following thyroidectomy Traces of iodine of course abolish entirely this effect of cabbage as it does with all other known goiter producing agents The mode of action of the goitrogenic factor is apparently by depressing tissue oxidations and it would seem, therefore, that the thyroid enlargement is the result of an attempt on the part of the thyroid to overcome this depression

We can now better understand the well known seasonal incidence of goiter, that is, in addition to a possible increase in the iodine intake during the summer months there is a greatly increased supply of the anti-goitrogenic substance from fresh growing plants which lessens the need for thyroid activity

If this normal constituent of the suprarenal cortex and sex glands is anti-goitrogenic, as all the evidence now

available seems to indicate, then we have the further insight into the influence of sex, puberty, pregnancy and the menopause on the development of goiter, and, as already indicated, we have also made a beginning in the solution of Graves' disease We now have something tangible regarding the nature of one of the factors which bring about the *relative* iodine deficiencies and subsequent thyroid enlargement in contradistinction to the thyroid enlargements dependent upon an *absolute* iodine deficiency

*To summarize*

Thyroid enlargement or goiter is apparently always due to a deficiency of iodine in the gland

On the other hand this deficiency may be primary or absolute as first suggested by the work of Chatin in 1850 and this would explain the increased incidence of goiter in relation to certain regions of the world

On the other hand the iodine deficiency may be secondary or relative, that is, the iodine intake may be normal, but owing to increased demands it is utilized so rapidly that it cannot be held in the thyroid in sufficient concentration to keep the gland from enlarging This condition may be readily produced in brook trout by feeding liver, in white mice by feeding cracker meal and in rabbits and rats by feeding cabbage or other Brassicae In the case of cabbage this relative iodine insufficiency is apparently produced by a powerful inhibitor of tissue oxidation Also a relative iodine deficiency may be brought about by a deficiency of certain anti-goitrogenic biological oxidation systems of the type of glutathione and hexuronic acid

Both of these substances are normally present in great concentration if not actually produced in the suprarenal cortex and sex glands. Stated more briefly, relative iodine deficiency goiter may be produced in rabbits either by cabbage with a high goitrogenic factor or a low antigoitrogenic factor.

These active oxidizing agents probably prevent thyroid enlargement indirectly by relieving the thyroid of excessive activity in bringing about biological oxidations, that is, a thyroid sparing action.

Iodine on the other hand is a direct anti-goitrogenic substance in that it is the essential constituent of the thyroid hormone and therefore prevents goiter by making it easier for the thyroid to produce an abundance of thyroxin.

Goiter due to a primary or absolute

deficiency of iodine is definite and easily understood, whereas goiter due to a relative or secondary iodine deficiency is more difficult to define, less understood and by far the most important since no animal with the ductless thyroid is free from the possible influence of *diet, pregnancy, puberty, and infections*. These conditions are as active in regions where there is a real iodine deficiency, that is, in regions of endemic goiter, as in non-goitrous regions and when thus combined the effects of *diet, puberty, pregnancy, menopause* and *infection* are greatly increased. So much emphasis has been laid on iodine deficiency in the etiology of goiter that there is a tendency to forget to bear in mind that the deficiency of iodine may be secondary as well as primary.

# The Relation of Experimental Rheumatoid Inflammation to Allergy\*†

By B J CLAWSON, M D, *Minneapolis, Minn*

THE microscopic lesions found in acute rheumatic fever have quite generally come to be considered characteristic (not specific) anatomic features of the disease both by those who believe the streptococcus to be the exciting agent and by those who believe that the disease is produced by an unknown virus. The lesions show mononuclear and multinucleated cells with vesicular or hyperchromatic nuclei (the so-called Aschoff cells), lymphocytes, plasma cells, eosinophiles, and a varying number of polymorphonuclear leucocytes.

Such inflammation, either in nodules or in irregular diffuse arrangement, has been described as occurring in the subcutaneous tissues, joints, tendons, galea aponeurotica, diaphragm, tongue and other muscles, tonsils, arteries, and in the valves, auricles, and ventricles of the heart.

The lesions in the myocardium as described by Aschoff<sup>1</sup> and Geipel<sup>2</sup> were interstitial submiliary bodies composed of large mononuclear or multinucleated cells with vesicular nuclei. The cytoplasm of these cells stained red with methyl-green pyronin. There

were lymphocytes, plasma cells in varying numbers, and occasionally polymorphonuclear leucocytes in the nodules.

The subcutaneous rheumatic nodules are localized areas of inflammation, mostly polyblastic in character, found in the loose connective tissue beneath the skin in some cases of acute rheumatic fever. The nodules have been studied microscopically by Hirschsprung,<sup>3</sup> Barlow and Warner,<sup>4</sup> Fitcher,<sup>5</sup> Frank,<sup>6</sup> Swift,<sup>7</sup> and others. There is a general agreement by these observers that the subcutaneous nodules consist of proliferating connective tissue cells and a cellular exudate of lymphocytes, plasma cells, polymorphonuclear leucocytes, and that in the center of most of the nodules there is a greater or less amount of a homogeneous substance consisting of necrotic material and fibrin. It is also agreed that anatomically and etiologically the subcutaneous nodules are similar to the nodules in the heart described by Aschoff, Geipel, and Coombs,<sup>8</sup> and to the type of inflammation found in other parts of the body in acute rheumatic fever.

This type of inflammation whether found in the myocardium, subcutaneous tissues, or any other part of the body has come to be considered by

From the Department of Pathology, University of Minnesota.

\*Read before the American College of Physicians, February 12, 1930.

many observers a specific reaction to the rheumatic virus. Others look upon these lesions as a polyblastic type of reaction common in rheumatic inflammation but not necessarily specific for the disease.

The first attempt to produce rheumatoid lesions experimentally was made in 1909 by Coombs, Miller, and Kettle<sup>9</sup>. They injected rabbits intravenously with streptococci isolated from the blood of patients with rheumatic infection and produced arthritis and myocardial lesions. Many of the lesions in the heart were nodular in form and showed the polyblastic type of reaction found in human rheumatic nodules in the myocardium. These authors decided that the difference existing between the experimental nodular infection and the human variety could be accounted for by the mode of entrance of the infectious agent in the two conditions.

Jackson<sup>10</sup> produced lesions in the interstitial tissues of the heart by injecting streptococci intravenously into rabbits. These nodular lesions were composed chiefly of large, irregular, mononuclear, and multinucleated cells which did not differ from those found in the heart in rheumatic cases.

Areas of polyblastic inflammation mostly perivascular in arrangement were observed by Small<sup>11</sup> in a papule developing at the site of an intradermal injection of a streptococcic vaccine.

By injecting streptococci, previously agglutinated, into the left ventricular cavity of rabbits I<sup>12</sup> was able to produce nodular polyblastic lesions in the myocardium in 21 cases out of 34. Microscopically these lesions showed

many multinucleated cells the cytoplasm of which stained red with methyl-green pyronin. Subcutaneous nodules<sup>11</sup> were also produced in a high percentage of cases by injecting strains of streptococci of low virulence in varying amounts at different intervals. With the larger doses abscesses developed. Morphologically the cells found in the smaller nodules were similar to those in human subcutaneous nodules and in human Aschoff nodules in the heart. It is evident that by injecting streptococci into the myocardium and the subcutaneous tissues of rabbits, lesions can be produced which morphologically show a marked similarity to the nodules found in the myocardium and subcutaneous tissues in cases of acute rheumatic fever.

Most of the animals used in the above experiments had been previously injected either intraarterially through the left ventricle of the heart or subcutaneously in one area with a mixture of streptococci and agar. Therefore, it could not be stated definitely whether the reaction in the nodules was influenced by existing immune or allergic reactions.

The phenomenon of allergy as related to rheumatic inflammation came into recent prominence through Swift's<sup>14</sup> work in a study of the hypersensitive (hyperergic) state of rabbits to streptococci, and a similar hypersensitiveness in people having acute rheumatic fever. Birkhaug<sup>15</sup> by skin tests also found that a high percentage of people having acute rheumatic fever were hypersensitive to streptococcic protein.

The following experiments were carried on in an attempt to determine

what part, if any, allergy or immunity played in the pathogenesis of the experimental rheumatoid lesions. If it is proved that animals hypersensitive to a bacterial protein, will respond to doses too small to call forth any reaction in nonsensitive animals and will react with the same type of cellular reaction which is produced by larger doses in non-sensitive animals, this may help to explain why in rheumatic patients who have been found to be hypersensitive to streptococci such extreme reactions take place when obviously very few organisms are present in the blood, joints, heart, etc.

The experimental lesions were produced by injecting streptococci (a rheumatic strain) in many places into the subcutaneous tissues of rabbits. One hundredth of a suspension of organisms in salt solution was injected into each of 10 places in the subcutaneous tissues in the backs of all animals on the right side and 1/1000 of a suspension was injected in a similar manner on the left side. The animals were killed 5 days after the multiple injections were made and the subcutaneous nodules, if present, were studied by gross and microscopic examination.

The following 3 groups were used in these experiments: (1) animals which had not been injected (normal animals), (2) animals which had been injected intravenously with streptococci (immune animals), (3) animals which had been injected subcutaneously in one area with agar at 45° C heavily seeded with streptococci.

The occurrence of an inflammatory reaction was slight in the 10 normal animals (Table 1). At least 10 injec-

tions were made on each side. Nodules were present with the larger doses in 7 of the 10 animals, but the number of nodules compared with the number of injections was small. Fourteen nodules out of a possibility of 100 (14 per cent) were present on the side injected with the larger dose and only 3 out of a possibility of 100 (3 per cent) on the side which was injected with the smaller dose. All of these nodules were small in size except in one case where the 3 nodules were of medium size. In only one of the 10 animals were there any nodules on the side injected with the smaller doses and these nodules were very small.

By microscopic examination the reaction in the smaller nodules was polyblastic in character similar to that in Aschoff nodules and subcutaneous rheumatic nodules in human cases. In the few larger nodules abscess formation was found in the center but a considerable degree of polyblastic reaction was always present in the periphery of the nodules.

Agglutinins were not present in any of the animals at the time of the multiple injections (Table 1). Five of the 10 rabbits showed agglutinins in dilutions not higher than 1:200 in the blood 5 days after the multiple subcutaneous injections. A titer of 1:200, as will be seen later in a study of the immune animals, was very low. No apparent relation existed between the presence of agglutinins and the number, size, or character of the nodules in the normal animals.

The animals in the second group (immune animals) had been immunized by an intravenous injection of streptococci. Multiple injections were

then made subcutaneously with the larger and smaller doses into the tissues of the backs of the different animals at intervals of 1, 2, 3, 4, 5, 6, 7, 8, 10, and 12 days. Little reaction occurred in this group as indicated by frequency, size, and character of the subcutaneous nodules in the 12 animals which had received the multiple subcutaneous injections in from 1-5 days after the primary intravenous immunizing dose. Nodules were present in 3 of the 12 animals. Only 4 nodules were seen out of a possible 120 (3 per cent) on the side injected with the larger dose. No nodules were present on the left side in which the smaller doses were injected (Table 1). The nodules were small and firm and by microscopic examination showed a polyblastic inflammation similar to that in the small nodules in the normal animals (Fig 1). It was evident that these 12 animals were not only not hypersensitive but that they had some degree of resistance since the number and size of the nodules were

less than those found in the normal animals.

In the 11 animals which had the multiple subcutaneous injections in from 6-12 days after the primary inoculation there was a marked reaction. Nodules were present in 44 per cent of the injections with the larger doses and in 15 per cent of the injections with the smaller doses. The nodules were more frequent, larger, and sometimes were found on the side of the animal injected with the smaller doses. The microscopic reaction in the nodules differed in no way qualitatively from that found in the normal animals.

Two factors may be thought of as the cause of the quantitative difference in the reaction in the 2 divisions in group 2: (1) the time of multiple subcutaneous injections after the primary immunizing inoculation, and (2) the degree of concentration of the immune bodies in the blood of the animals. In the first division the time was from 1-5 days and in the second from

TABLE 1. RELATION OF EXPERIMENTAL SUBCUTANEOUS NODULES IN NORMAL, IMMUNE, AND ALLERGIC ANIMALS TO THE AGGLUTINATING TITER OF THE SERUM OF THE ANIMALS

Kinds of Animals	No	Percentage of Subcutaneous Injections Producing Nodules		Maximum Agglutinating Titer	
		Right Side with Larger Doses	Left Side with Smaller Doses	At Time of Multiple Injections	When Animals Were Killed
Normal	10	14	3	0	1:200
Immune A	12	3	0	1:200	1:6,400+
Immune B	11	44	15	1:6,400	1:6,400+
Hyperimmune	8	9	2	1:256,000	1:300,000
Allergic	12	73	60	1:400	1:400

Immune A—Animals receiving the multiple subcutaneous injections in the back from 1-5 days after the immunizing intravenous injection.

Immune B—Animals receiving the multiple subcutaneous injections in the back from 6-12 days after the immunizing intravenous injection.

Hyperimmune—Animals which had received 4 intravenous injections at intervals of 5 days before the multiple subcutaneous injections in the back were given.

6-12 days Allergic reactions are likely to take place in from 6-15 days after an initial injection In the first division the concentration of antibodies was low never being above 1:200 at the time of multiple subcutaneous injections In the second division the concentration was high 1:6400

To determine whether a hypersensitivity rather than the high antibody content in the serum was responsible for the greater frequency and larger nodules, 8 animals were highly immunized by giving 4 intravenous injections at intervals of 5 days These animals were then given the multiple subcutaneous injections in the back In the 8 animals there were 9 nodules out of a possibility of 160 In 9 per cent of the injections with the larger doses and 2 per cent of the injections with the smaller doses there were nodules The microscopic structure of the nodules was similar to that seen in the nor-

mal and the other immune animals The agglutinating titer was high 1:256,000 and 300,000 Since so few nodules developed in the 8 hyperimmunized animals it was evident that the increase in frequency and size of nodules in the second division of the immune animals was not due to the increased concentration of the antibodies but that it was most likely due to an allergic reaction as in animals made hypersensitive from an injection of streptococci in agar

The hypersensitive animals were injected in one place subcutaneously with 5 cc of melted agar at 45° C heavily seeded with streptococci An abscess regularly developed at the point of inoculation Multiple subcutaneous injections were made from 12-15 days later as in the normal and immune animals

The gross reaction in this group of animals was pronounced With the larger dose all but one of the

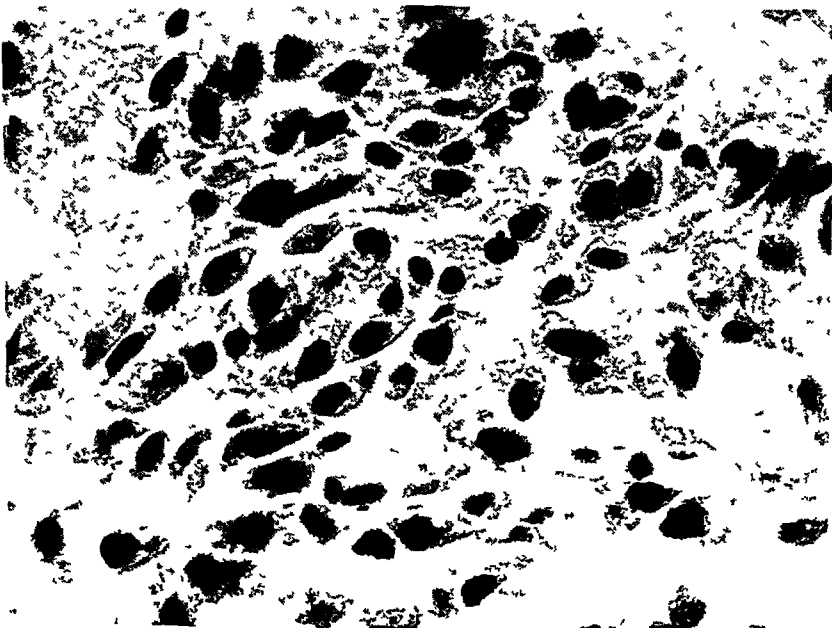


FIG 1 Polyblastic nodule

12 showed subcutaneous nodules and with the smaller dose nodules were present in all but 3. With both doses there were many nodules most of which were large and showed abscess formation. With the larger dose 73 per cent of the injections showed nodules and with the smaller dose 60 per cent (Table 1). It is obvious that the reaction in this group was definitely more extensive than in the other 2 groups.

The microscopic type of reaction showed a more pronounced exudation than in the normal and immune animals especially in the large nodules which were regularly abscesses. The smaller nodules showed the polyblastic type of reaction.

It was evident that the greater degree of reaction or hypersensitiveness so pronounced in this group was not due to a high antibody content since the agglutinating titer in none of the animals was ever above 1:400. The hypersensitiveness seemed to depend upon something which was not present in the normal and immune animals. The conspicuous thing which was present in group 3 and absent in groups 1 and 2 was the primary abscess resulting from the injection of the agar heavily seeded with streptococci. Something bound up with the abscess seemed to be responsible for the hypersensitiveness. What this substance or condition associated with the abscess is, apparently has not been determined by workers in immunity.

In conclusion it may be said that in the normal animals few lesions were produced. In the immune animals when the subcutaneous inoculations were made before the sixth day after

the immunizing inoculation practically no lesions were present. Those animals in which the subcutaneous injections were made in from 6-12 days showed a greater frequency than did the normal animals. This greater reaction was probably due to allergy since other animals highly immunized from several intravenous injections did not have the increased reaction. On the other hand a retardation was evident. In the hypersensitive animals gross lesions, often large abscesses, were practically always present with both the larger and smaller doses.

Two types of cellular reaction were noted in all 3 groups: (1) the exudative, generally with necrosis and abscess formation, and (2) the polyblastic reaction. The cells chiefly found in the exudative reaction were polymorphonuclear leucocytes. In the polyblastic lesions there were regular and irregular mononuclear and multinucleated cells with basophilic cytoplasm, plasma cells, eosinophiles, lymphocytes, and often a few polymorphonuclear leucocytes. In some nodules the polyblasts appeared to have wandered in, while in others they appeared to have developed from the existing cells in the region of the nodules.

No difference could be detected in the character of the polyblastic reaction in the nodules in the normal, immune, or hypersensitive animals. Polyblastic inflammation free from abscesses was less common in the hypersensitive animals since the nodules were larger and the larger nodules regularly became abscesses.

It appears evident that the polyblastic type of reaction which is charac-



teistic of the lesions in human rheumatic cases does not depend primarily upon a hypersensitive state when produced experimentally in animals. This reaction may be produced with larger doses in both normal and immune animals. However, doses which in normal or immune animals have no noticeable effect or produce only small firm polyblastic nodules, will in hypersensitive animals stimulate the production of

definite nodules many of which are extreme enough to be definite abscesses. The relationship between allergy and the polyblastic type of reaction, as seen in human rheumatic and experimental streptococcic lesions, appears to be not a qualitative but a quantitative one. This quantitative relationship may help to explain the pathogenesis of human rheumatic lesions in many cases.

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# Embolectomy\*†

By WILLIAM T PEYTON, M D, *Minneapolis, Minn*

**A**N attempted embolectomy was first reported in 1895, still this operation is quite rare in this country. Less than 20 cases were reported from the United States and Canada according to Pemberton in 1928. Reports are rare because the diagnosis is not made, or if made, it is not recognized as a surgical condition. It is the internist or general practitioner who sees these patients at the time when operation offers most, and an opportunity has been lost if he does not call the surgeon before gangrene has appeared. It is with the hope of keeping the subject before the profession until it becomes common knowledge to all that this accident is an urgent surgical condition that this paper is written.

In recent literature this subject has been so repeatedly reviewed that no attempt will be made here to give a complete review, but merely to stress some features of special interest to the internist and give a brief report of two cases, with one successful result. A complete review is to be found in the report of Einar Key (*Acta Chir Scand*, 1921-22) or in that of Marco

Petitpierre (*Deutsche Zeit fur Chir*, 1928).

The largest group of collected cases, i e, 118, were reported by Petitpierre in 1928. Of the 95 cases collected by Key of Sweden up to 1925 only about one-half were included by Petitpierre because the others have not been published, being personal communications to Key. A great number of embolectomies performed have never been published, and no doubt they were for the most part unsuccessful cases, since one is more prone to report a successful case. Therefore when Petitpierre reports 34 or approximately 29 per cent of all cases successful in these 118, it is more favorable than if all cases were reported.

A thrombosis is practically always the source of an embolus. A calcified plaque becoming dislodged from the aorta is the only exception. This possibility is mentioned in the literature, but has not been the proven cause of any case. In 6,140 autopsies studied by Bull, there were 15 cases of extremity embolism. Thrombus formation was demonstrated in one or more of the cardiac cavities in 13 of these cases, the primary thrombosis was presumably in the aorta in the other two. Heart disease, he concludes, is the chief source of embolism, aneurism of

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†From the Department of Surgery of the University of Minnesota

the aorta and arteriosclerosis are only seldom the source. The primary thrombus may be dislodged *in toto* and its site at autopsy impossible to determine. The primary disease was mentioned in 10.4 of the 118 cases collected by Petitpierre. It was heart disease alone in 60 cases (approximately 58 per cent), arteriosclerosis in 4, syphilis in 2, it followed operation, delivery, or abortion in 23 cases and it followed infection in 11. The primary disease in the other cases was one each of widely different diseases. Mitral stenosis is the most common mitral disease causing embolism. It was present in 18 of Petitpierre's collected cases. Venous thrombosis and arterial emboli of the extremities were associated in only two of his cases and an anatomically open foramen ovale was found in only three of the cases collected by Petitpierre.

Embolism was demonstrated in other parts of the body as well as the extremity in all except one of the 15 cases found in autopsy material reviewed by Bull. These additional emboli were found in the lungs, nine times, kidneys, nine times, spleen, seven times, brain, four times, and in the intestine once. A complete search for evidence of other emboli should not be neglected where embolism is suspected in the extremity. This multiplicity of emboli was demonstrated in the case of an elderly, extremely obese woman with diabetes who developed an embolus in the popliteal artery while a patient at the University Hospital. A large vegetation on the aortic valve and an abscess at the base of the left lung was demonstrated at

post mortem, this abscess was due to an infected embolus.

Emboli lodge at the bifurcation of an artery or the origin of a large branch, occluding both vessels as a rule. Vessel spasm, according to Petitpierre, is set up by the irritation of the embolus in the vessel, and this spasm plays a rôle in fixation of the embolus. Improvement sometimes seen in an extremity within the first 24 hours after lodgement of the embolus, he states, is probably due to relaxation of this spasm which lasts several hours, always less than 24 hours. Sufficient collateral circulation cannot develop in this short time to explain the improvement.

The frequency with which the various arteries are affected is well illustrated by Figure 1, taken from Petitpierre (*Deutsche Ztschr. f. Chir.*). This illustrates the location frequency in his 118 cases.

Gangrene follows more often if the circulation is occluded by an embolus than if it is occluded by ligature of the artery at the same point, because at the bifurcation of an artery or at the origin of a large branch emboli usually lodge, and both vessels are occluded, secondary thrombus formation results, extending rapidly in a distal direction and a clot also extends proximally to the origin of the next large branch. The collateral circulation is still further occluded by this thrombus. Beginning secondary thrombus formation was observed by Key as early as two hours after lodgement of an embolus. A secondary thrombus 86 centimeters long was present 12 hours after the lodgement of the embolus in a patient operated by Sandberg. Sec-

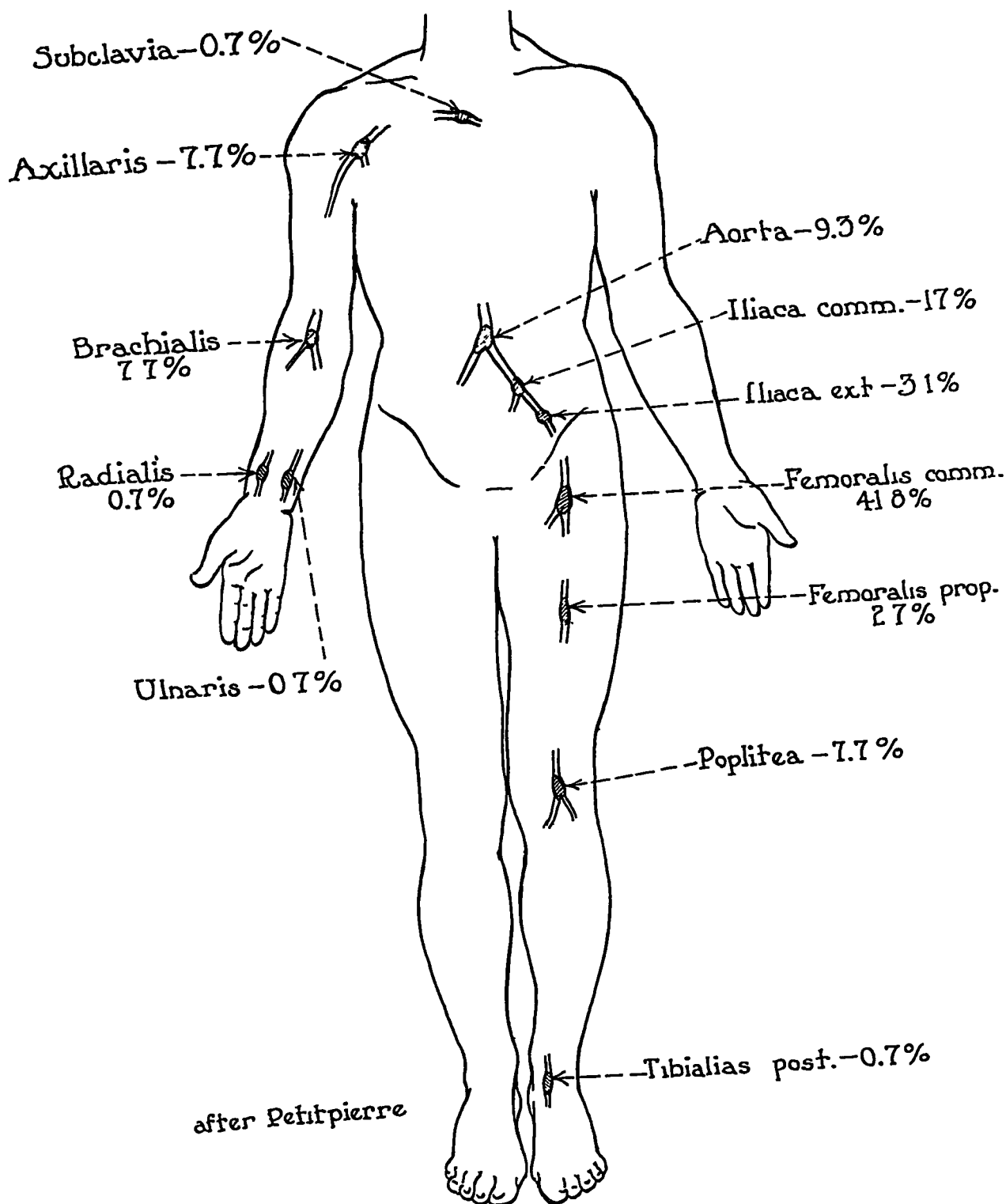


FIG 1 Frequency of embolism in different arteries

ondary thrombosis, however, may be slow to form. There was no thrombus in a patient operated by Ipsen two days after the occurrence of the embolus. The proximal secondary clot does not form until there is complete occlusion of the lumen of the vessel by either the embolus itself or the secondary thrombosis.

The prognosis depends upon many factors. Death in most cases is cardiac, i.e., the primary disease. The age of the patient and arteriosclerosis influence the prognosis in embolectomy. The intima in arteriosclerosis is easily injured and thrombosis occurs after operation. A patient 82 years of age, however, has been successfully operated. Massage to break up the clot and cause it to pass more distally is advised by Key, if there is high grade arteriosclerosis. According to Nystrom, eight or ten cases have been published where massage was followed with good results.

Early operation is most important in embolism. Delay allows the embolus to become adherent. Removal is then more difficult and the intima more likely to be injured causing thrombosis after operation. Secondary thrombosis when extensive may be very difficult or impossible to remove.

The importance of an early operation is demonstrated in the following table of results compiled by Petit-pierre.

Time between occurrence of embolus and operation	Circulation restored		Circulation not restored	
	Cases	Percent	Cases	Percent
1-5 hours	24	58	19	42
6-10 "	15	68	7	32
11-15 "	6	46	7	54
16-20 "	2	29	5	71
21-24 "	1	14	6	86
Over 24 "	8	24	26	76

Similar results are reported by Key, who concludes that the prognosis should be good if operated in the first 10 hours but rapidly becomes worse thereafter.

In the upper extremity the prognosis is better than in the lower following occlusion of the vessels by an embolus. That gangrene is less frequent in the upper extremity following occlusion of the vessels by ligation has been demonstrated by Wolff and also by Heidrich. There are however other reasons why the prognosis is better in the upper extremity. Surgical approach is more difficult in the abdominal aorta, the iliac vessels and the popliteal vessels. A greater portion of the arterial bed is cut out of the circulation in an embolus of the lower extremity and this (first mentioned by Wildhopf) throws an extra load on the heart which is the site of the primary disease in most cases. A comparison according to location in 17 cases operated in the first ten hours after the occurrence of the embolus is given by Key. Eight were successful. His results are given in the following table.

Site of Embolus	Successful Cases
Axillary or brachial artery	3/4 of all cases
Femoral artery	1/2 of all cases
Iliac artery	1/3 of all cases
Aorta	1/7 of all cases

Multiple emboli, if present in an extremity, prevent complete restoration of the circulation after removal of the

most proximal one. Careful examination of the circulation should, therefore, be made immediately after operation, and if another embolus is present this should also be removed.

The symptoms of a typical case are pain, usually sudden and severe. There is a cold feeling in the extremity, a heaviness in the extremity and loss of sensation. Objectively there is a discoloration of the skin, cyanosis or an appearance described as marbling of the skin. There is a lowering of the temperature in the distal portion of the extremity with a sharp line of demarcation between this and the warmer skin more proximal. There is a loss of reflexes and a variable amount of paralysis. Pulsations in the arteries are absent. The embolus may be palpable.

In the differential diagnosis, embolism is most likely to simulate thrombosis. The onset in embolism, however, is more sudden, there is heart failure and cardiac thrombosis or some other cause for an embolus as infectious disease or recent operation. Emboli in other parts of the body should be looked for because they are almost always multiple. In thrombosis a long history of such symptoms as the extremity going to sleep, neuralgia, rheumatic pains, and circulatory changes with cyanosis of the extremity are common. Hematomyelia and transverse myelitis may simulate embolism. There are no circulatory changes in these conditions, but there are neurological findings sufficient to differentiate them from embolism.

The treatment is immediate operative removal of the embolus and secondary thrombus if this is present.

Massage is indicated only in certain selected cases.

Two embolectomies have been performed in this Clinic recently with one successful result. They are here briefly reported.

*Case I* The patient was a young woman 22 years of age. She had heart trouble for 12 years according to her history. The present attack began with vomiting 18 days before admission to the Hospital. This vomiting continued for a period of two weeks. She noticed her heart was beating with unusual rapidity and that she was cyanotic the day after the onset of this vomiting. A physician was called and she was given digitalis. The pulse was 150 and irregular. The next day the pulse was 80 but irregular. Three days later she was given quinidine, and the following day the pulse was regular. There was less cyanosis and dyspnoea. She steadily improved from this time until the day of her admission to the Hospital. A sharp cramp-like pain occurred in her abdomen the day she was admitted. Immediately numbness, pallor, and pain occurred in the lower extremities. Approximately 30 minutes after their onset, the abdominal pain and the symptoms in the right leg disappeared but the pain in the left leg continued with such severity that morphine was administered. (The embolus at this time became dislodged from the bifurcation of the aorta and passed into the left iliac artery.)

Physical examination revealed a young woman very dyspneic and cyanotic, with no palpable radial pulse and a very irregular apical pulse varying between 110-130 pulsations per minute. A loud systolic murmur was heard at the apex transmitted through the axilla. All extremities were cold and cyanotic. The popliteal pulse was interpreted to be faintly palpable in both legs. The left leg was entirely anesthetic and paralyzed.

Arteriotomy was performed immediately after admission to the Hospital. An embolus and thrombus were found in the left iliac and femoral arteries. These were removed but circulation was not established in the extremity. A more distal incision

was made and more thrombus was removed. Still the circulation in the left leg was not re-established and the patient died a few hours later.

**Case II** A man 58 years of age was admitted to the Hospital in January 1926, complaining of a swelling in the right scrotum which proved to be a hydrocele and a hernia. He also complained at that time of dyspnea which had been present for 20 years. This dyspnea made it impossible for him to sleep in a prone position. The cardiac condition was considered to be an aortic stenosis with aortic insufficiency and cardiac decompensation.

Because he had developed edema and ascites he returned in May, 1927. In June 1927, he was re-admitted with cardiac decompensation and ascites.

Again with edema and ascites he was admitted in May 1928, and it was demonstrated at this time that he had auricular fibrillation.

With the same complaint of edema and ascites he was re-admitted September 5, 1928. Six days after admission to the Hospital he developed an embolus for which embolectomy was performed. The attack began at 3 a. m. with severe pains in the left thigh and leg. A distinct pallor of the foot was evident and there was no pulsation in the vessels. Anesthesia of the distal portion of the leg was present with paralysis of all the muscles below the knee. The skin of the foot and leg was cold. Nine hours after the onset of his pain the patient was operated for embolus which was thought to be lodged in the femoral artery at the profunda femoris. At this site one embolus was found, after the artery was exposed but while it was being elevated the embolus became dislodged and then pulsations were present throughout the exposed portion of the femoral artery. Pulsation was also noted in the popliteal artery at this time although it had not been present before the operation. The embolus had become dislodged and passed down to the bifurcation of the popliteal artery into the anterior and posterior tibial arteries.

The patient was again taken to the operating room five hours later and the popliteal

artery exposed. The embolus was in the terminal one and one-half inches of the popliteal artery. It was removed, and there was free flow of blood from arteriotomy wound when compression of the artery either above or below the incision was released. Immediately after operation the anesthesia and paralysis were found to have disappeared almost completely. Pulsation was present in both the popliteal, tibial, and dorsalis pedis arteries. An uneventful recovery followed and he was discharged from the Hospital 39 days after operation (October 20, 1928).

He returned December 11, 1928, with ascites and swelling of the left leg. There was good pulsation in the arteries of the left foot at this time. He was discharged January 12, 1929. For ascites he returned again March 18, 1929. There was no swelling of the left leg at this time. Ascitic fluid was again removed and he was discharged March 26, 1929. He died the next day at his home. This attack began about three hours before death with pain in the right leg and the left elbow. The family physician who attended him at this time considered embolism the cause of death.

## SUMMARY

1 Embolectomy of the arteries of the extremities is not recognized as an urgent surgical condition by many internists and general practitioners.

2 The primary disease in most cases is cardiac, and of the various cardiac diseases mitral stenosis is the most common cause of embolism.

3 Embolectomy should be performed as soon as the diagnosis of embolism is made and certainly before gangrene has appeared.

4 A single embolus is rare. When suspected, search should be made for evidence of emboli in lungs, kidneys, and spleen.

5 Emboli lodge at the bifurcation of large vessels or the origin of a large branch.

6. Secondary thrombosis follows the lodgement of an embolus. This obstructs the collateral circulation.

7. For re-establishment of the cir-

ulation the prognosis becomes rapidly worse if the patient is not operated within approximately ten hours after the embolus has occurred.

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# Preliminary Results of Resection of Sympathetic Ganglia and Trunks in Seventeen Cases of Chronic "Infectious" Arthritis\*

By LEONARD G. ROWNTREE, M.D., ALFRED W. ADSON, M.D., and  
PHILIP S. HENCH, M.D.,  
*Division of Medicine and Section on Neurologic Surgery,  
The Mayo Clinic, Rochester, Minnesota*

**R**ESECTION of lumbar sympathetic ganglia and trunks for the relief of so called chronic infectious arthritis (rheumatoid arthritis, arthritis deformans) of the lower extremities was first employed in June, 1926. The operation was performed by Adson at the request of Rowntree. The rationale for the procedure, and the immediate results of the operation on the first patient, and the subsequent course of the disease have been presented by Rowntree and Adson. The degree of relief experienced in the lower extremities, particularly in the feet, caused the first patient to request earnestly a somewhat similar procedure to relieve the pain and disability in the upper extremities. Hence, in November, 1928, resection of the cervicothoracic sympathetic ganglia and trunks was done in an attempt to relieve the pain and disability of the arthritis of the upper extremities. These results likewise were recorded and in another article, the results in the first

six cases of our series were described. The relief of disability of the joints, during the first months after operation was sufficiently satisfactory so that it was decided to determine further the limitations and value of resection of sympathetic ganglia and trunks in arthritis of the type generally believed to be of the chronic, nonspecific, infectious form.

To date, eighteen bilateral operations of the type mentioned have been performed on seventeen patients.

One patient underwent both cervical and lumbar procedures. Of these, fifteen operations concerned the lumbar, and three the cervicothoracic sympathetic apparatus. Although this represents a fairly considerable experience, the number of cases is too small and the time elapsed too short to permit of other than tentative opinions regarding the selection of patients for the procedure, its indications, its contra-indications and its results.

Although this report will include a summary of the results in all cases to date (seventeen cases; eighteen operations) the data regarding the last elev-

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en will be given only by way of a general statement, for in them, less than six months has elapsed from the time of operation. The report also will deal with the further progress, since our last report, of the first six patients who were subjected to the operation. These have been emphasized because the time which has elapsed since operation in each instance is sufficiently long (six months to three and a half years) to permit of some idea as to the nature and permanency of the changes induced, and the correctness of our criteria for the selection of cases. They include, furthermore, patients who illustrate what are probably different phases of chronic infectious arthritis (periarticular, chondro-osseous phases)

#### REPORT OF CASES

*Case 1.*—A woman, aged thirty-four years, with crippling, generalized polyarthritis of six years' duration, was subjected to resection of the lumbar sympathetic ganglia and trunks in June, 1926, and to resection of the cervicothoracic sympathetic ganglia and trunks in November, 1928. Her progress has been definite. Since dismissal she has suffered somewhat from tenderness and pain between the shoulder blades in the region of the surgical scar.

In the autumn of 1928 she wrote that she had not had any further pain in the lower extremities, and that she still felt occasional twinges of pain in the left wrist on washing dishes and in the right shoulder on carrying heavy weights. About this time also, she informed us that she was conferring with the president of the railroad concerned in an accident which she had sustained and requested from us a letter concerning the nature of her illness and its relation to the railroad accident. During this period, when a pension was pending, she wrote that she had suffered a relapse of the arthritis.\*

\*Nervous stress and strain probably play a part in the pathogenesis of this form of

chronic arthritis. A second patient has not done as well as we expected; a question of disability insurance is concerned. A third patient suffered a relapse during the serious illness of her mother.

Following the receipt of a letter announcing that she had been awarded her pension, she wrote that she had improved greatly. The relief of the condition in her lower extremities may therefore be considered complete and that in the upper extremities may be graded as very considerable. In this case, the arthritis was very largely periarticular.

*Case 2.*—A girl, of Greek parentage, aged sixteen years, with polyarthritis of the lower extremities of two years' duration underwent resection of the lumbar sympathetic ganglia and trunks and returned after two months, at that time she was able to walk a distance of 100 to 200 feet without assistance. Improvement continued so that at the end of five months after operation she could walk comfortably a distance of four city squares and had taken up dancing again. Pain had almost disappeared from all the joints of the lower extremities. This also represents a case of the periarticular form of arthritis. Development of arthritis elsewhere in the body has not been reported.

*Case 3.*—In a woman, aged forty-four years, the condition ran a definitely febrile course, with extreme anemia, marked swelling of the joints, striking muscular atrophy, and no improvement of the condition of the joints after seven and a half months of treatment in hospital. Following the cervicothoracic operation in May, 1929, and prior to her dismissal on the forty-fourth day, the condition of the upper extremities was markedly improved, the swelling decreased at least 50 per cent, and the function of the hands and arms was restored at least 50 per cent. Her condition continued to improve considerably for a number of weeks. At the end of four months she wrote that the condition of her hands was becoming stationary. At the expiration of seven months she reported that her general condition was decidedly improved, but that that of her legs was unchanged.

and that she still was bedridden. Later, she stated that she had had an exacerbation of the attacks and that her left hand was somewhat worse. However, she also stated in the same letter that she wanted to return for the lumbar operation for relief of the arthritis in her legs.

*Case 4*—A man, aged twenty-six has experienced no relief of his main complaint, pain in the right hip. The arthritis was of long duration, twelve years, had resisted all forms of medical treatment, was destructive, and there were marked bony changes. Since his operation he has reported the continued presence of large, swollen lymph nodes below Poupart's ligament on the right side, and marked pain in the hip and lymph nodes on every attempt to move the right leg. To date, at least, the result here must be regarded as a complete failure so far as his chief disability is concerned.

*Case 5*—A woman, aged twenty-one years, has shown definite improvement despite the diagnosis of bony ankylosis in the knees and hips. She returned home after a period of four to five months in the hospital. She then was able to walk alone and unassisted, although she had been completely bedridden for two years prior to operation. She has written that she still has considerable pain in her knees, and especially in her right hip, but that, once she is placed on her feet, she can walk around the house comfortably. She has suffered one mild exacerbation of arthritis. Although there is still marked limitation of motion, she has acquired an unexpected degree of motion in the knee, and, to a less extent, in the hips. The results to date have been satisfactory, especially in view of the bony changes and the marked degree of ankylosis.

*Case 6*—A woman, aged thirty-four years, with generalized arthritis, returned home eight weeks after resection of lumbar sympathetic ganglia and trunks. Her condition was markedly improved so far as all the joints of the lower extremities were concerned and she could walk up and down stairs, a feat that had been impossible to

her for the preceding eight years. Her physician, who visited the clinic two months after her return, reported continued marked improvement and stated that she went about everywhere with little, if any, trouble in the feet and legs. However, she replied personally, at the end of six weeks, saying that she had had an exacerbation of arthritis at the time that a sinus in the wound had discharged a stitch. There was some involvement of the legs, but this was not comparable to the exacerbation in the arms. The arthritis is progressing in the upper extremities, but its progress has slowed up remarkably in the legs.

*Comment*—The results after six months are unusually satisfactory in at least three of the six cases. The degree of improvement was greatest in cases of the periarticular type. The acceptance of the other three patients for operation was in the nature of clinical experimentation. Their cases were advanced, had not responded to other treatment, and in the light of our present experience would not now be accepted for operation.

The results in the remaining eleven cases can more appropriately be covered by a simple statement. Marked relief from pain was encountered in many of the cases of the periarticular type but relief was less marked and slower in onset in cases with osseous changes.

If all seventeen cases are considered, in six, chondro-osseous changes were definite or advanced, as indicated by roentgenologic evidence. In not a single instance was recovery complete in this group. In our opinion, the relief from pain, however, justified the procedure in most instances. Considerable improvement was noted in five. Of the eleven cases of the periarticular type, marked improvement

was seen in nine. In fact, six of these have had but little pain in the extremities since operation, and in all except two the improvement has been marked.

#### POSTOPERATIVE COMPLICATIONS

Complications following operation have not been serious except in one case. Ileus developed in two instances following the lumbar operation, and in one case was rather extreme. Rather profuse diarrhea was marked in three other cases, but in no instance was it serious. In one case, following resection of cervicothoracic sympathetic ganglia and trunks rather mild pleurisy developed, and in another case, mild pleurisy developed on the twelfth day following the lumbar operation. Following the lumbar operation on two patients a rather acute exacerbation developed in the metacarpophalangeal joint of the right thumb. Pains in character resembling that of erythromelalgia were observed in two cases over a period of approximately a week, but these were readily controlled by elevation of the part concerned. Our first patient has suffered considerably from pain below the shoulders, about the operative scar. Personnel neuritis was unmasked by the operation in one case. On resumption of activity, myalgia has been noted in most of the cases. It is, however, not severe and is of short duration. Deaths have not occurred in the series either immediately after operation or in subsequent months or years.

#### SELECTION OF PATIENTS FOR OPERATION

Selection of our first patient was founded chiefly on the presence of

neurocirculatory changes in the extremities and long-standing chronic arthritis which apparently was unresponsive to the usual methods of treatment. There were no gross bony alterations in the joints. The hands and feet were cold and clammy as well as swollen and painful. Because of the warming up of the extremities after resection of sympathetic ganglia and trunks in Raynaud's disease, it seemed reasonable to expect a similar result in the cold extremities of patients with arthritis, and it was hoped that with the additional warmth, pain would cease. The selection of the first patient seems justified.

In selecting patients with chronic infectious arthritis for resection of cervical sympathetic ganglia and trunks, six requisites have been adopted up to the present time.

1. The arthritis should be chiefly periarticular in type, with little, if any, bony alterations (destruction or hypertrophy) except atrophy, and with little, if any, deformity except that resulting from periarticular changes.

2. The patients should present neurocirculatory changes evidenced objectively by cold, clammy, sweating hands or feet, and subjectively, by a feeling of coldness, numbness and tingling.

3. The circulatory deficiencies must be capable of correction, indeed of overcorrection, under the influence of release from control of the sympathetic apparatus. The possibility of such correction can be demonstrated by the "vasomotor index" (Brown); a definite increase of the cutaneous temperature of the extremities perhaps three to five times greater than the m-

crease of the temperature of the mouth after typhoid vaccine (50,000,000 bacteria) has been given intravenously

4. The patient should be, preferably, aged less than thirty-five years, and not more than forty or forty-five years

5. The arthritis should have been progressive and the main disability should be confined to the extremities, particularly to the hands and feet

6. A reasonable period, probably a minimum of six months, of intensive, systematic treatment by the more established, less radical procedures should have been allowed

*Exceptions in selection of patients* — In the majority of our seventeen patients, all six of the requisites were met. In six cases, exceptions were made in that patients were accepted for operation, although the joints of the extremities involved presented fairly marked bony changes. In these cases, the exceptions were made deliberately because of lack of improvement in the condition after a prolonged period of intensive treatment, because of the painful, progressive character of the arthritis, and in order to test out the limits and values of the operation

In one case, because of the rapid progression of the arthritic disability, the economic circumstances necessitating an early return to work, and failure of previous treatment to give appreciable benefit, operation was advised rather soon after the onset of the arthritis

How far the eventual results will justify these exceptions cannot be stated. In some cases, the results to date seem to justify their selection,

whereas in other cases failure materially to alter the disability must be recorded. This indicates that until more is known regarding the use and limitations of resection of sympathetic ganglia and trunks for cases of chronic infectious arthritis, acceptance of patients who do not present the six criteria mentioned should be made with caution in order not to discredit unjustifiably the value of the operation for that type in which it seems to be particularly suitable

It will be seen that the ideal subject for this procedure is one who is young, who has the periarticular (rheumatoid, atrophic) variety of chronic infectious arthritis, and that chiefly in the hands or feet. To a less degree the subject in which the elbows and knees are affected is suitable. In our comment we shall deal with the indications for resection of sympathetic ganglia and trunks for infectious arthritis of the spinal column, hips, and shoulders, and to its extension into the field of chronic traumatic, chronic gouty, and chronic senescent arthritis

#### POSTOPERATIVE TREATMENT

The postoperative treatment is of considerable importance. Because of the diminution or absence of pain in the joints, there exists the temptation to attempt a program of overactivity. In the results of the treatment it will be seen that in certain instances pain is more favorably and more rapidly affected than some of the other phenomena of the arthritis, such as swelling and stiffness. Pain is but one signal, and when it is removed, care must be taken not to overexercise the joints until subsidence of the other phe-

nomena indicates the appropriateness of increased activity. Excessive weight-bearing should be avoided, especially in obese persons. Physiotherapy, active and passive motion, and massage are desirable subsequent to operation, since they complement the increased heat in the affected members, which is the result of the operation. When necessary, mild analgesics may be supplied.

In general, a program of conservatism is desirable, and the amount of activity should be guided by the condition of the patient; the pain on exertion serves somewhat as an index. Certain orthopedic measures may be indicated as supplementary measures, such as manipulation of joints and extension. In cases of arthritis of the knees, with previous flexion deformities, braces may be necessary until improvement takes place. When the patient has been bedridden or confined to a wheel chair for a considerable period of time, walking should be undertaken, at first with the aid of a walker, and later with crutches or a cane, until the patient's equilibrium and confidence are restored. The application of correct shoes is important. It will be recalled that painful, flat feet, associated with disability elsewhere, are complained of by a group of patients who consult orthopedists.

In general, foci of infection will have been entirely removed before the patient presents himself as a possible subject for resection of sympathetic ganglia and trunks. If they have not, care should be taken that all foci of infection are removed before dismissal of the patient. Full instructions in

physiotherapy to be applied at home are given to the patients and their own efforts should be supplemented by an adequate program of physiotherapy to be given under professional supervision.

## COMMENT

*The nature of the circulatory alterations in arthritis.*—Unfortunately, the nature of the circulatory changes in arthritis is not definitely known. Hence, it would be unwise to make assumptions concerning them. We have spoken of them in an earlier communication as vasospastic phenomena, without, however, attempting to explain their nature.

We can make our position clear, perhaps, by first acknowledging that we do not know with certainty that this form of arthritis is infectious, and that we do not understand the nature of the derangement of the circulation or the part that the nervous system plays in these changes. The known facts are as follows. Prior to operation, the hands and feet are cold and clammy and bathed in sweat. Studies of transference of heat from these extremities, in the Stewart-Keggereis calorimeter, indicate a low normal value. Mottling and cyanosis of the skin of the hands and feet are common. The study of the capillaries of the nailfolds reveals capillaries larger rather than smaller than normal, and with a very slowly moving blood stream. Trophic changes, particularly of the finger nails and toe nails, are very common, as is atrophy of the muscles. The feet are often painful at rest, particularly on compression and on walking.

After resection of sympathetic ganglia and trunks, the following changes are noted. The hands and feet become warm, pink and dry. The temperature increases anywhere from 5 to 10°C. Sweating ceases. Pain decreases immediately and in some instances disappears almost completely; disappearance is earliest in the periphery of the extremities, and later, to a lesser degree, in the more proximal joints.

Transference of heat, as measured in the calorimeter, increases anywhere from 100 to 500 per cent. Under the microscope the capillaries now appear narrower, and the flow of blood is markedly increased. Trophic changes tend to disappear. Swelling about the joints tends to subside and the muscles tend to return to normal size and function. The nails become normal in consistency and appearance.

From what has been said, it is not likely that the arthritic changes are brought about by spasm of the large arteries. Professor Krogh, with whom the problem was discussed, felt that the most likely explanation was that there is an arteriolar constriction, with peripheral dilatation of the capillaries. This constriction ceases after resection of sympathetic ganglia and trunks and permits a more rapid and normal flow of blood, with increased tonus in the walls of the capillaries. For the time being, at least, we will refer to these changes simply as "neurocirculatory" without any attempt to explain them.

*The use of resection of sympathetic ganglia and trunks in the general field of arthritis*—Resection of sympathetic ganglia and trunks is not indicated in all forms of polyarthritis. Hench has

classified arthritis, on the basis of presumptive evidence, as follows (1) infectious, (2) traumatic, (3) senescent, and (4) chemical, for example, gouty. This classification is particularly valuable for within itself it suggests a rational basis for treatment.

The group of cases of chronic arthritis with which we have dealt may belong to the infectious type, although this is not yet proved. Acute involvement of the joint precedes these chronic manifestations in certain instances, but by no means in all. These neurocirculatory manifestations are secondary to what appears to be infection, in some instances, but in other cases they seem to be primary in origin. Whether primary or secondary, they may respond to resection of sympathetic ganglia and trunks and when present they constitute an indication for the procedure.

It is possible that in other forms of arthritis, resection of sympathetic ganglia and trunks may be of value. This is a matter that can be settled only by time and clinical experimentation. The rational indications for its use in these other forms of arthritis are not yet determined. Until more is known, we wish to advocate the employment of resection of sympathetic ganglia and trunks only in the periarticular form of arthritis that has been described and especially in cases in which the chief disability is in the peripheral parts of the extremities, and generally in cases in which there are neurocirculatory phenomena. Otherwise, it may be employed in a haphazard and irrational way and quickly may come into disrepute. In certain instances of infectious periarticu-

lar arthritis in the extremities, the appearance of neurocirculatory phenomena may be rather long delayed after the onset of the disease. In some of these cases, the rapidity of progression, degree of disability and pain, and lack of response to other treatment may justify the operation in spite of the absence of definite neurocirculatory alterations.

#### SUMMARY AND CONCLUSIONS

1 These seventeen cases serve to indicate the value and limitations of resection of sympathetic ganglia and trunks in the treatment of chronic infectious arthritis.

2 They demonstrate that the procedure is applicable both to the upper and to the lower extremities, and that the best results are obtained in the periarticular type of arthritis, associated with neurocirculatory alterations. In such cases, the relief from these vasomotor alterations, such as coldness, and sweating, is extremely gratifying. Indeed, if the operation is performed in an anatomically correct manner, sweating should be completely absent subsequent to operation.

3 The cases demonstrate that definite restorative influences are supplied to combat the trophic changes and atrophy of muscles such that in some cases function is restored to a considerable degree.

4. Our experience indicates that the effect of resection of sympathetic

ganglia and trunks lasts for a period of at least six months and has lasted more than three and a half years. It promises to be of permanent value. The best results are obtained in the hands and feet; the results in the knees and elbows are less marked and slower in developing. The effect of the procedure in the hips and shoulders seems considerably retarded. The operation for arthritis of the hips and shoulders alone seems as yet not justifiable.

5 The presence of bony changes, revealed by roentgen ray, particularly in the knees and hips, suggests a less hopeful, indeed in some instances a hopeless, outlook. However, even when ankylosis is completely or partially established, pain while the subject is at rest may disappear, and pain on active motion may be alleviated wholly or in part.

6 Failure of the operation has been most apparent in joints, particularly in painful hips which still were movable but in which there were marked osseous changes.

7 For the present at least, we advocate this procedure for the one type that has been herein described, mainly periarticular arthritis with evidences of neurocirculatory phenomena, and which react to administration of typhoid vaccine with a high vascular index. The result in some of these cases, as far as the hands and feet are concerned, seem gratifying.



# Remarks on Chronic Infections\*

By ALLEN K. KRAUSE, *The Desert Sanatorium, Tucson, Arizona*

THE time-limits set for the presentation of this address have led the author to restrict his attention to a particular type or group of chronic infectious processes rather than to attempt a synoptic discussion of certain broad features, mainly etiological, of chronic infections in general, the purpose that inspired the original title of his paper

This particular group of chronic infections involves the lungs. It represents processes that are essentially focal, that is, localized. Its etiology is dubious, save that this is certainly non-tuberculous and its pathology, for months, years and even decades, may be no less dubious. Its consequences, there is reason to suppose, may be grave indeed,—to anticipate a bit,—we are wondering whether often we may not here be dealing with the precursors or originators of conditions which, as finished or incidental processes, later present themselves to us as bronchiectasis, or bronchopneumonia,—recurrent or periodic bronchopneumonia,—or asthma, or even abscess. This group of pulmonary infections will never come to autopsic observation except through some acci-

dental unrelated cause, when, if it did, it is questionable whether routine examination would detect a definite pathological condition. At its slightest or mildest it is doubtful whether examples of the group will overly impress the medical attendant, unless he has become alive and alert to their existence. At its worst he is likely to decide that he is dealing with bronchiectasis or chronic "pneumonia."

The clinical histories of patients with the type of pulmonary infection in question may vary much in details, but their general tenor is not uncharacteristic. Indeed, it is close attention to clinical history that above all else is likely to put the physician on the track of their recognition. Out of a rather checkered clinical past there usually emerges the prominent item that the subject—usually child or young adult—has been oversusceptible to colds, perhaps for years, and characteristically increasingly so as regards both number and severity. Then, in not a few, the recurrent winter cold takes a turn that is manifestly of more moment than a cold and is (rightly so) considered as bronchopneumonia. Following this appear persistent changes in the lungs, most often in base or mid-lung, when now these more permanent residua are conceived of as having originated in the recent pneumonia

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and as being the latter's unresolved remains. The point is that old focal changes had in reality antedated the pneumonia and that the latter has been merely an acute incident in the more or less prolonged course of a chronic process.

We may attempt a type-history, emphasizing that this will have many variants. Very often, if not most frequently, the patient is a child, six, eight, or a dozen years old, yet with years of medical concern, especially as to nose and throat, behind him. He was a healthy baby until a first acute illness like whooping cough or measles. After this he gradually, even insidiously, slipped into the category of "delicate child." Successive winters were sure to find him easy, and easier and easier prey to catching cold, until the approach of the cold season was anticipated with dread. In time, winter came to mean one long stretch of "bronchitis," so called, punctuated with acute febrile periods that put the child to bed. With the coming of warm weather, the bronchitis improves and fresh colds become fewer, until by midsummer the child is symptomatically sound, and he keeps symptom-free until the first pronounced autumn weather ushers into the inevitable new "cold."

The ordinary child of this type comes out of the winter a good deal run down, with blood, weight and vigor under par, and during the summer again builds up, often to normal capacity. The very fact that such a child in time comes to be over-protected and coddled, in efforts to ward off the taking of cold, tends to soften him and increase his susceptibility to fresh attacks.

Meanwhile this child has usually made the rounds of the nose and throat clinics, and, usually too, has at one time or another had tonsillitis, adenoids, otitis media or sinusitis. Often one or several of these conditions has been chronic and recurrent. Often again all treatment has been directed to these appendages of the respiratory tract, with the idea that they alone have been responsible for the symptoms that rise manifestly from some disturbance lower down. One by one these upper respiratory conditions are corrected or removed, and often with a fair measure of success as the recurrent "colds" lessen or abate. But only too often by the time the throat, nose and ears are attended to, the over-susceptibility to colds seems to have become fixed, and these go on with even increasing frequency and severity.

It is now that an over-severe "cold" gets out of bounds and takes on the ear-marks of a bronchopneumonia. Now are found, perhaps for the first time, localized pulmonary changes, which remain after recovery from the acute illness. And now also the patient resumes his former condition of delicate constitution, and chronic bronchitic symptoms, but with the difference that he is now known to have a patch of râles or increased X-ray density out from the hilum or toward the base, where none was known to exist before, and this is presumed to be a spot left by his pneumonia.

Or it may be that, without suffering a pneumonic attack, symptoms of asthmatic nature make their appearance; and that these lead to unusual scrutiny of the chest; and that now a

midlung or basal pathological process is disclosed

There is increasing evidence that in many of these children with over-susceptibility to colds, pulmonary changes, located more below midlung, have existed for a long time, and that they are the site whence originates the trouble that has afflicted the child for years. Under present conditions of practice it is likely that in the very great majority of cases they go unrecognized until the incidental occurrence of some more serious and better defined malady, such as bronchopneumonia or asthma, which sends the physician to a more thorough and assiduous examination of the chest. We believe that, if ordinarily practiced earlier, closer attention to the chest would bring to light many more focal processes of this type in patients who have not gone as far as the more severe manifestations. But we are also beginning to wonder whether many of these patients may not for a long time have small more or less permanent foci of non-tuberculous infection whose anatomical presence defies detection even by X-ray.

In other words, is there such a condition as permanent pulmonary change set up by infection of a chronic and clinically persistent or recurrent nature that is not demonstrable by ordinary diagnostic methods? If so, how frequent is it and how often can or does it assume more significant proportions? The reason for asking such questions is that it is only by supposing the actual occurrence of such focal changes as probable and not uncommon that we can come to an understanding

of a series of clinical events that is by no means rare.

There is, for instance, the patient of varied age, as often as not a vigorous young adult, who comes down with a hard cold, marked by the usual symptoms and three or four days of moderate fever. The disease runs its usual course and convalescence is normal in every respect except that we are disturbed by the persistence of a few râles in a small localized patch at the base. On the strength of this finding we keep an otherwise recovered patient in bed, hoping that the râles will disappear. But they do not disappear promptly. They do not disappear with weeks in bed, as meanwhile a restive patient clamors to be let up and about his daily life. Time and again they will not fade out entirely until the coming of summer with its established warm season. Then, and not until then, does the chest become clear.

There is nothing particularly remarkable about this relatively common incident, nor would it be difficult to understand if this were all there always was to it. But some of these cases become puzzling when we find them in the throes of a fresh winter cold, say, the next winter. We observe the same symptoms, the ordinary ones of a hard cold. We hear râles. But—and this is remarkable—the râles are in the identical spot where we detected them the year before and whence they slowly disappeared. Further, the patient stages the same performance of a year previously, that is, carries the râles until summer with its sun and warmth rids him of them.

Some of these patients also gradually slip into a condition of permanent pulmonic signs, summer as well as winter, and of increasing disablement by recurrent winter colds. Arrived at this point, their general course is not materially different from that of the younger patient sketched above.

It is obvious that established bronchiectasis must have an antecedent development, and we ask ourselves whether these minor changes may form the nidus or the earlier phases of such a later more serious process. We also speculate as to the pathological (anatomical) nature of these essentially slight changes. They cannot be regarded as an ordinary chronic bronchitis, a diffuse involvement of the air-passages, for the lesions in question are essentially focal, thus resembling the beginnings of tuberculosis. But in such foci what tissues are involved and how are the component structures of the lung modified? Moreover, does there exist a permanent focal infection of the lung with microorganisms nesting continuously, to flare and erupt clinically from time to time?—or do the recurrent winter attacks of "cold" mean that with repeated fresh infections from without the newly received germs are accustomed to focalize in the same spot,—perhaps because this is a damaged and therefore a weakened patch of tissue?

It is difficult to entertain the last supposition. Limited time will not permit of an analysis of probabilities; but it is much more in line with newer concepts of infection in general to presume that a permanent and fixed and at the time perhaps latent focus of infection reactivates and takes on new

clinical significance under the influence of the obscure biological and immunological agents which we know are set in motion by even the common cold. Our concepts of chronic infections have been changing radically of recent years, and among these newer ideas none is of more significance than the growing opinion, continually being fortified by new evidence, that clinical recurrences of varied features of infectious processes represent, not fresh infections, but renewed phases of clinical activity of infections long present but at intervals concealed. The case was long ago settled for syphilis, and is now universally accepted. That for tuberculosis had a rockier road, but the weight of evidence and general opinion is now overwhelmingly for it. That for gonorrhoea, essentially and significantly one of our most superficial infections, is well established, as too is the quite comparable case for diphtheria. Evidence accumulates that recurrent rheumatic fever and acute endocarditis represent acute phases,—episodes,—incidents in the life-history of a chronic, apparently deep-seated infectious process. And a growing acquaintance with the clinical histories and manifestations of these patients characterized, among other features, by an over-susceptibility to catching cold, engenders the conviction that many of them are in reality harboring relatively permanent, usually basal, chronic infectious processes.

If there are relatively permanent small foci of non-tuberculous infection in these patients, what are we to think regarding their pathological (anatomical) character? Sooner or later some of them come to observation, es-

pecially X-ray, as irregular patches of increased density, when, with or without râles on physical examination, they may be supposed to be mainly sclerotic formations in which have been involved the several elements of pulmonic structure,—bronchi, bronchioles, alveoli, etc. We have in mind now one particular case,—that of a child, five years old, who in June showed just this structural change after four years of recurrent winter colds, and who in August, following exposure, developed bronchopneumonia, confined to the patch in question. This now suddenly extended its boundaries. The impression conveyed was as though an old and relatively quiescent non-tuberculous infection had “sloped over”, as it were, into pneumonia. Recovery from the latter was marked roentgenologically by a gradual drawing in of the area affected by the pneumonia as well as by a more rapid and complete disappearance of râles.

But what are the earliest changes,—earliest though on occasion lasting perhaps for years,—in such a focus which merely gives out a few persistent râles following a heavy cold, and this recurrently for several years with intervals of essentially normal breath-sounds between? Clinically there has never been a symptomatology to allow a diagnosis of bronchopneumonia. Perhaps, though, this is merely a question of extent of involvement, and it may be that essentially pneumonia had existed,—a pneumonitis or alveolitis, let us say, covering a very limited territory indeed. And, when signs persist in this region after prompt symptomatic recovery from the acute hard cold, it is not too much to suppose that,

if not alveoli, then small air-passages—bronchioles as well as bronchi—have undergone changes that persist. Complete resolution has not terminated the acute inflammation; something more than mucosa had been involved, and rather lasting focal changes in the walls of the air-passages have resulted. We may speculate as to fibrosis with a concurrent limited lymphangitis of these structures. And, if this is the condition, how can a few alveoli escape participation in the process?

Let this go on for some years, and let it moreover be exacerbated and added to by ever-recurring “colds,” and we arrive at an appreciation of how the field is prepared for the origin and development of localized bronchiectasis; or how are established foci that under proper excitants can set up bronchopneumonia; or how, more rarely, focal abscesses may arise, or how may be prepared the mechanism for “asthmatoïd” phenomena.

For it is only a step from permanently damaged bronchioles to weakened bronchiolar walls, with focal bronchiectasis in the offing, as happens in focal pulmonary tuberculosis (We are now thinking in anatomical terms only.) Or, if nests of microorganisms dwell on within these foci, occasional flarings into bronchopneumonia would seem inevitable, whence, in a minimal proportion of cases, further development to at least miliary abscess would be just as inevitable.

Clinically, we have been particularly interested in the asthmatic side of some of these cases. It is characteristic that symptoms of asthma do not appear at the beginning, but only after there has been a fairly long history of

the recurrent "colds," with presumably the chance for chronic pulmonary changes to develop. Now come the sudden attacks of coughing or wheezing, precipitated often by abrupt exposure to cold air or even by stepping with bare feet on a cold floor. As for the "asthma" there may be anything from transient wheezing to prolonged and severe attacks that superficially resemble classical bronchial asthma.

But we have thus far been unable to bring ourselves to identify what here seems like asthma with the classical disease. Features of hypersensitiveness have been conspicuous by their absence, as have too those of heredity. We are much more impressed by the probabilities of the mechanical side of the case. We remember the rich endowment of nerves and ganglia that Miller has pictured existing in the human lung, and recall particularly those findings of Miller's in which, in connection with focal pulmonary disease, nerves and ganglia were observed to be involved,—*"enmeshed"* as it were,—in the inflammatory or infiltrative process. Sometimes it was the nerves of supply to bronchial mucous glands, a finding that suggested an effect on bronchial secretions. We have seen long periods of symptomatic quiescence in these cases interrupted by sharp asthmatic attacks during which these foci, free from signs for a long time previously, gave out a wealth of signs, as meanwhile the temperature rose and the rest of the lung was relatively quiet. We wonder therefore whether a focus, placed right as regards nerves and ganglia, may not precipitate asth-

matic symptoms through merely mechanical irritation.

Relatively early and minor focal infectious processes, such as we have been discussing, must be of every degree of duration, extent and significance. Many, perhaps most, no doubt disappear completely without ever having caused illness of any moment. But, as representing foci that may go on to some of the most serious of pulmonary diseases, they are to be regarded seriously. Many will no doubt question the dictum that they should be viewed at least as seriously as the minimal or early focus of tuberculosis that has thrown out warnings of activity. Yet when one sees the patient who gradually progresses to recurrent pneumonia or bronchiectasis one inclines to so radical a position. As in tuberculosis the time to get the condition therapeutically is at the beginning, a prime reason why the condition should be recognized in its incipency. Even though not the trace of an anatomical change can be demonstrated, we must suppose that where there are long-continued basal râles, or râles at the same spot with recurrent colds, there must be a pathological focus,—a focus that represents a relatively permanent infection, harboring living microorganisms that await only the favoring agents to be aroused to renewed activity.

Even after the process is fairly extensive anatomically, it may be râle-free over long periods. But this need not mean that it has lost all capacity for mischief. With a fresh "cold" it again sends out sounds in abundance and gives out all the signs of acute re-inflammation. These foci are prob-

ably never of no further moment until they have been completely healed and fibrosed

It is particularly important to attempt the healing of these processes in children. Fresh exacerbations and progressions to the point of bronchiectasis can forecast as sinister a prospect as active tuberculosis. Nor should one postpone serious treatment until the appearance of one of the graver consequences of these foci.

Their treatment is tedious, and under ordinary conditions unsatisfactory in any environment that promotes the catching of colds, especially winter colds. Sinuses, middle ears, throats, etc., should all be accounted for medically and surgically, and the body be built up through attention to the elements of good hygiene and such aids as codliver oil. If all this succeeds, well and good. But if, as often happens, it does not, then our sovereign resort is to climate.

Climate for this condition means that region where the chances of catching fresh colds are reduced to a mini-

mum. The process is essentially one that is kept stirred up by recurrences of winter colds. Resort to a warm and preferably dry climate is therefore the treatment of choice. In principle, treatment aims at promoting scarring which is to be accomplished mainly by avoiding focal exacerbations activated by acute colds.

Yet even in the ideal warm winter climate, and when fortunately fresh colds are avoided, the infection, once it is well established, does not yield readily. Successful treatment requires months,—of at least the whole of one winter,—and it may take several years. Lacking the irritating effects of fresh colds the patient may become asymptomatic at once and remain so throughout a winter. Yet, as in tuberculosis, exacerbations are possible as long as the process is not completely healed, and once embarked upon the healing of the focus it is a pity to terminate treatment short of this being thoroughly performed, if this is possible. Ideally, it is this accomplishment, and this alone, that should set the term to climatic treatment.

# Tetany\*

By JONATHAN MEAKINS, *Montreal Canada*

**T**ETANY has been recognized as a clinical entity since the classical description by Clarke in 1815. It appears with great frequency in the older literature but has become of progressively less importance as a distinct symptom complex during the past thirty years. It has been reported in epidemic form in both Europe and America, when it appeared to have a seasonal occurrence particularly in March and April and affected young men between the ages of sixteen and twenty-five, seldom appearing in women.

Like many syndromes of the past, the etiology of which was not understood, it was classified as a distinct disease. It has now been established that 'tetany' is usually only a sign of a more obscure disturbance of metabolism. Where at one time it was considered rather common, its rarity now may be judged by the fact that in the general teaching hospitals attached to the McGill Medical Faculty, out of 219,000 admissions only fifty cases with a primary or secondary diagnosis of tetany were recorded. Of these, thirty-six cases occurred in the Departments of Pediatrics. It is true that a number of instances may not have been recorded, as in recent years

the tendency has been to consider it but as a symptom and not as a distinct entity.

Tetany may be defined as "a condition in which the neuro-muscular system exhibits a pathological hyperexcitability to stimuli of normal intensity". The first successful attempt to correlate this condition with a metabolic disturbance was that of MacCallum and Voegtlin<sup>1</sup>. They found in cases of tetany resulting from extirpation of the parathyroid glands that there was a lowering of the blood serum calcium which was in proportion to the severity of the tetanic symptoms. The next important contribution was the demonstration of a low serum calcium and a relatively high serum phosphorus in the tetany associated with rickets. This brought these two well-defined causes of tetany into conformity.

It had long been known that tetany was sometimes associated with pyloric obstruction, gastrectasis and other chronic abdominal conditions which resulted in persistent and long-continued vomiting. But with improved gastro-intestinal diagnosis and surgical therapy these cases became extremely rare. With the introduction of the intensive alkaline treatment of peptic ulcer they re-appeared and it soon was demonstrated that their occurrence depended upon the produc-

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tion of an alkalosis, the blood calcium remaining normal or even being increased. Investigation of the occasional cases of chronic vomiting revealed a similar alkalosis from the excessive loss of hydrochloric acid while an almost identical series of events occurred in violent hypernea causing extreme carbon dioxide elimination. The last method produces the most prompt occurrence of tetany due to alkalosis on account of the ease with which carbonic acid can be removed from the tissues and thus produce a cellular alkalosis. This can be done in a few minutes in comparison to the days which may be required to produce the same degree of alkalosis by the oral administration of alkalis or by vomiting. Even the intravenous injection of alkaline solutions requires some time before tetanic symptoms develop, even though there may be a considerable alkalosis in the plasma. This is explainable on the grounds that the alkaline salts diffuse but slowly into the cells while the removal of carbonic acid from them can be accomplished with great rapidity.

The next class of case, to be elucidated with which tetany is associated, were chronic intestinal disorders,—namely, sprue and allied conditions. Among the other signs of sprue there is a disturbance of the calcium balance with a decrease in the serum calcium. In advanced cases symptoms of tetany develop which may be corrected by the raising of the serum calcium. Blumgart<sup>2</sup> in 1923 reported two cases with chronic diarrhoea and mal-absorption of fat who had tetany while under observation. In one case the serum calcium and serum phosphorus were reported—the former was low, being

5.3 mgms per cent, while the latter was normal, being 2.6 mgms per cent. In addition, both cases showed a pronounced reduction in the bicarbonate reserve. In one case where the large bowel was examined, megalocolon was found.

In 1929 Holmes and Starr<sup>3</sup> reported five similar cases of chronic diarrhea, mal-absorption of fat, megalocolon and tetany. In all these cases there was a pronounced decrease in the serum calcium and the tetanic symptoms were only controlled by the use of parathyroid hormone. In none of these cases was the bicarbonate reserve or the pH of the blood reported. There seems no doubt that these cases are closely allied to sprue and that the symptoms of tetany are due to the disturbance of the calcium balance.

Probably the only other condition where there is a distinct reduction in the serum calcium is in chronic nephritis. In many instances this is so low as to warrant the expectation of the appearance of tetany were this a specific cause of the hyper-excitability. The work of Salvesen and Linder<sup>4</sup> and Peters and Eiserson<sup>5</sup> shows that the variation of calcium should not be considered by itself alone but must be interpreted in conjunction with the serum protein and inorganic phosphorus. Peters and Eiserson give the following equation to correlate these three components in the serum—
$$\text{Ca} = -0.255 \text{ P} + 0.566 \text{ protein} + 7,$$
and furnish an alignment chart for ready determination of the expected value of one of these if two be known. In the cases of renal disease examined they found that the correlation of these three substances made close agreement when plotted on their chart.

The cases of tetany reported in the present series may be classified as follows:

- 1) Tetany with rickets and low serum calcium, 36 cases, or 72 per cent.
- 2) Parathyroid deficiency and low serum calcium, 3 cases, or 6 per cent
- 3) Chronic gastro-intestinal disease with fatty stools and low serum calcium, 1 case, or 2 per cent
- 4) Excessive alkali intake with alkalosis, 3 cases, or 6 per cent

In this series no case of true gastric tetany was found. All of those with a past history of peptic ulcer were not vomiting immediately before the onset of the tetanic symptoms but were taking large doses of alkalis.

There are remaining seven cases which do not conform to the usual classification of tetany. One case was admitted with the signs and symptoms of hyperthyroidism and showed definite signs of tetany before operation. The serum calcium at this time was 7.8 mgms per cent. A sub-total thyroidectomy was done and she made an uninterrupted recovery. Since the operation there has been no return of the tetany although the serum calcium remains at a low normal level, varying between 7.8 and 8.4 mgms per cent, and all indications of hyper-excitability to mechanical and electrical stimulation have disappeared.

Finally there are six cases which form a group by themselves. These are all women varying in age from 17 to 28 years. In none of them was there any evidence of thyroid, parathyroid, gastric or intestinal disease.

In all cases there were the usual signs of tetany—intermittent or continuous rigidity of the muscles of the upper, lower or body extremities, the "accoucheur's hand", or the "main en grippe" was always present. The usual signs of mechanical irritability of neuromuscular systems such as Trousseau's and Chvostek's sign were positive. Some of the spasms were more violent than others and in a number of instances general anesthesia was necessary to remove the painful contractions. The more unusual signs such as strabismus, conjugate deviations of the eyes, contracture of one or both orbicularis oculae, dysphagia, aphonia, laryngeal stridor, explosive vomiting and diarrhea, spasmodic retention of urine, were present in a more or less pronounced degree in all cases. These signs with the altered response to the interrupted and constant electrical current afforded no doubt that these patients were suffering from what is usually considered to be tetany.

There were present, however, none of the usual diseases with which tetany is ordinarily considered to be associated. More intensive study still further failed to reveal any of the usual chemical changes which were to be expected. The examination of the serum showed the calcium phosphorus and protein to be in normal amounts and to have a normal ratio to each other. The basal metabolism was also found to be within normal limits. There was no history of chronic diarrhea, while the stools did not contain an excessive amount of fat.

As all the usual causes of tetany had been explored, attention was then directed to the more unusual causes. It was considered possible that an un-

explained and intermittent alkalosis might have given a clue to the onset of the symptoms, and this was borne out by finding an increased carbon dioxide combining power of the plasma. This ranged in upper limits of normal, being between 65 and 75 cc volumes per cent, but this was not considered in itself of sufficient magnitude to initiate the symptoms.

There have frequently been recorded cases of so-called hysteria and other psychic disturbances accompanied by respiratory abnormalities and tetany. As to whether these conditions had a definite biochemical foundation has never been fully explored. Likewise in the sequelae of encephalitis lethargica, tachypnea or polypnea associated with tetany has been reported. These cases have still to be investigated from a biochemical point of view.

On further investigation there was found to be in four of the cases here reported a common sequence of events at the initiation of the attacks. They were almost identical in each case. The onset was characterized by an acute pain in the lower sternum or upper epigastrium with a sensation of constriction of the chest. This pain was usually of the most agonizing character and, as the patients all stated, they felt as if their chests were completely filled with air and that they could not expire, this in spite of the fact that laryngeal spasm was present in only one case. The respirations were rapid, ranging between 40 and 60, of a shallow character and at times respirations ceased in complete inspiration. In one case inspiratory apnea occurred over a period of fifteen seconds. After this respiratory pain and abnormal rhythm had con-

tinued for a variable length of time tingling in the hands and feet followed by general tetanoid spasms occurred, and the respiratory distress became progressively more severe. In three of the cases a general anesthetic was administered in order to obtain relief of symptoms. In the fourth case the respiratory distress and cyanosis during the initial attack was so alarming, and examination of the larynx appeared to reveal redness and swelling of the larynx, that a tracheotomy was performed. This gave but temporary relief. Unfortunately an estimation of the bicarbonate reserve was not done at this time but subsequently it was found, during an interval between attacks, to be 75 cc volumes per cent, which indicated a distinct alkalosis. This patient had repeated attacks of respiratory distress each one associated with tetanoid spasms, cyanosis and great apprehension. When she came under our observation we were immediately impressed by the character of the respiratory disturbance. This suggested the probable production of an uncompensated gaseous alkalosis by the polypnea initiated in one who already had a moderate alkalosis. Therefore preparations were made to carry out a therapeutic test as to the probability of this assumption. When an attack was again precipitated by excitement it was allowed to become well established and then the patient was made to inhale a mixture of 5% CO<sub>2</sub> and 95% oxygen. Within 1 minute the symptoms of tetany completely disappeared although the pain in the lower sternal region still remained. A careful examination at the time of these attacks revealed the fact that abdominal respiration had practically ceased,

that the abdominal muscles were held in a rigid condition and it was surmised that the diaphragm was in a state of tonic contraction. Unfortunately an X-ray examination during an attack was not possible

It is not suggested that these cases are the after-math of encephalitis lethargica nor that they can be properly classified as hysteria. It seems probable that they are cases of unexplained alkalosis with an unstable nervous control. Whether this instability may be the result of the alkalosis or not is at present not clear but there seems to be a close association between the two conditions. Attempts have been made to institute the attacks by forced breathing, but this so far has been unsuccessful chiefly, we believe, through the resistance of the individuals to undertake real hyperpnea. At no time have we been able to increase the respiratory volume while at rest beyond 8 litres per minute.

It has already been mentioned how easy it is theoretically to produce a cellular alkalosis by increased elimination of carbon dioxide and it is surprising that more cases of tetany due to this cause, independent of those occurring as a sequel of encephalitis lethargica, have not been reported. It is our belief that this is a distinct clinical entity and that after further investigation a definite biochemical explanation is forthcoming. The work of

Dale and Evans<sup>6</sup> with excessive pulmonary ventilation producing a rapid removal of carbon dioxide showed that the pH of the blood in dogs could be changed from 7.48 to 7.82 in twenty seconds. Co-incident with this there was a rapid drop of blood pressure which action could be reversed by the same excessive ventilation but using expired air. They demonstrated that this fact was not generally due to the change of pH in the circulating blood but was due to the actual extraction of CO<sub>2</sub> from the tissues, and particularly from the tissues of the central nervous system. We are not inclined to believe that the pH of the blood under all circumstances actually reflects the intra-cellular conditions, and particularly when dealing with such a highly diffusible substance as carbon dioxide.

Up to the present much attention has been paid by clinicians to acidosis and its associated deleterious action on the central nervous system, but as yet little attention has been paid to the opposite disturbance of acid-base equilibrium, namely alkalosis, particularly when resulting from too rapid removal of carbon dioxide. It produces what is commonly known amongst physiologists as an uncompensated gaseous alkalosis,—a condition which is not tolerated by the nervous system and may be fraught with most disastrous results.

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# Splenic Puncture as a Diagnostic Procedure in Infancy and Childhood\*

By JULIUS H. HESS, M.D., *Chicago, Ill*

**A**T no period during life is an enlarged spleen so common a finding as in infancy and childhood. However, emphasis should be placed on the fact that an enlarged spleen frequently does not have the same significance in early life that it does in adults. This applies more especially to the acute splenomegaly of moderate degree as seen during acute infections and the chronic splenomegaly associated with nutritional disturbances.

In a review of the literature numerous classifications of splenomegaly are found, some of them quite complete but none entirely satisfactory from

either an etiological, pathological or clinical standpoint. Our limited knowledge of etiologic and pathogenic factors render such a grouping impossible. In this discourse an attempt will be made to formulate a classification of splenomegalies from the standpoint of the clinical value of splenic puncture as a diagnostic procedure. To properly interpret the material obtained through puncture of the spleen the normal cytology must be established.

From a pathologic consideration the increase in size of the spleen may be due either to hyperplasia of its normal structural elements, the storage of

## CLASSIFICATION OF SPLENOMEGALIES IN CHILDHOOD FROM THE STANDPOINT OF SPLENIC PUNCTURE

- I Splenomegaly Associated with Dysfunction of the Hematopoietic System
  - A Anemias secondary to defective mineral metabolism—3
  - B Anemias secondary to defective regeneration (von Jaksch's)—3
  - C Anemias secondary to increased blood destruction
    - 1 Hemolytic Icterus, congenital and acquired
    - 2 Sickle Cell anemia, as distinguished from sickleemia (Cooley)—5
  - D Purpura Hemorrhagica—2
  - E Leukemias—2
- II Splenomegaly Associated with Storage Disorders of the Reticulo-Endothelial System
  - A Diabetic lipemia
  - B Niemann-Pick's disease (Lipoid Histiocytosis-Bloom) (Spleno-hepatomegaly-Pick)—7
  - C Gaucher's disease—7
- III Splenomegaly Secondary to Bacterial and Spirochetal Infections
- IV Protozoal and Parasitic Splenomegalies
- IV Protozoal and Parasitic Splenomegalies

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abnormal substances or the development of a new tissue which may be inflammatory or neoplastic in nature

By means of splenic puncture, qualitative changes in the cell structure of the splenic pulp are readily recognized. The interpretation of quantitative changes in both normal and abnormal cells is less definite. Comparative studies of the cellular elements in the circulating blood and the splenic material will aid in clarifying the activity of the spleen in some of the blood dyscrasias.

Cells obtained through splenic puncture can best be evaluated through a conception of—first, cells derived from the normal splenic substances and, second, elements brought to the spleen by the circulating blood.

The splenic substance consists of Malpighian bodies and splenic pulp. The Malpighian bodies are ovoid or spherical structures and comprise a reticulum infiltrated with lymphocytes. In infants and children a lighter central zone can be distinguished. This is composed of large pale cells with large reticular nuclei showing at times active mitotic changes. The cells of the outer zone of the Malpighian bodies show the typical structural characteristics of the mature lymphocytes in that they have a more pyknotic nucleus smaller in size and deeper staining. They also have less cytoplasm than the more centrally situated cells.

The splenic pulp is the tissue proper of the spleen and contains a variety of cells. The cells of the supporting reticulum are large, frequently branched and closely associated with the reticulum fibre. Besides this group, of tissue cell origin, one occasionally

encounters cells of the sinus endothelium. Histiocytes (frequently called pulp cells or splenocytes) are found isolated as free macrophages. These cells are endowed with marked phagocytic properties. Under physiological conditions the phagocytosis is directed against worn out erythrocytes but in pathologic processes they may be further concerned in the disposal of bacteria and protozoa and the storage of abnormal products of metabolism.

In addition to the cells above described, cells derived from the circulating blood are also found in the splenic pulp. This is possible because of the unique vascular arrangement of the spleen. The arterial blood instead of passing directly into the veins by the usual capillary connections is allowed to flow freely in the splenic pulp. Thus in the normal splenic pulp we may expect to find erythrocytes, polymorphonuclear leucocytes, lymphocytes, monocytes and blood platelets. While in blood dyscrasias the cells may be representative of changes in the blood forming organs.

#### TECHNIC OF SPLENIC PUNCTURE

In the presence of a large spleen it can be performed without difficulty. With the patient in a recumbent position, the spleen is held firmly against the abdominal wall with the left hand. In children a needle about 3 cm in length, attached to a well ground 2 or 5 c c glass syringe is used. We have found a 22 gauge needle with a blunt bevel most satisfactory as with such a fine needle there is less danger of hemorrhage. In young children at least a partial anesthesia or the use of sedatives is recommended, because of

the danger of tearing the spleen in a struggling child. Only moderate suction should be used. The plunger should not be released until the needle is withdrawn, otherwise the splenic content will be lost through return of the piston by the negative pressure created. Under no circumstances should more than a few drops be withdrawn. Following puncture 0.2—0.3 cc of 1:1000 adrenalin solution should be injected subcutaneously. This causes contraction of the splenic capsule. Splenic puncture is contraindicated in the presence of prolonged bleeding or coagulation time.

#### STAINING THE SPLENIC SMEAR

The combined May-Grunwald-Giemsa has been used for our staining

In addition brilliant cresyl blue was used to emphasize the reticulation of the red cell.

#### Classification of Splenomegalies in Childhood From the Standpoint of Splenic Puncture

##### I *Splenomegaly Associated With Dysfunction of the Hematopoietic System*

###### A Anemias secondary to defective mineral metabolism

Insufficient mineral deposits may result from a deficient iron intake or insufficient utilization as seen in simple nutritional disorders. These factors may account for the anemias with splenomegaly present in many cases of rickets.

In both these types there is only moderate splenic enlargement. Splenic

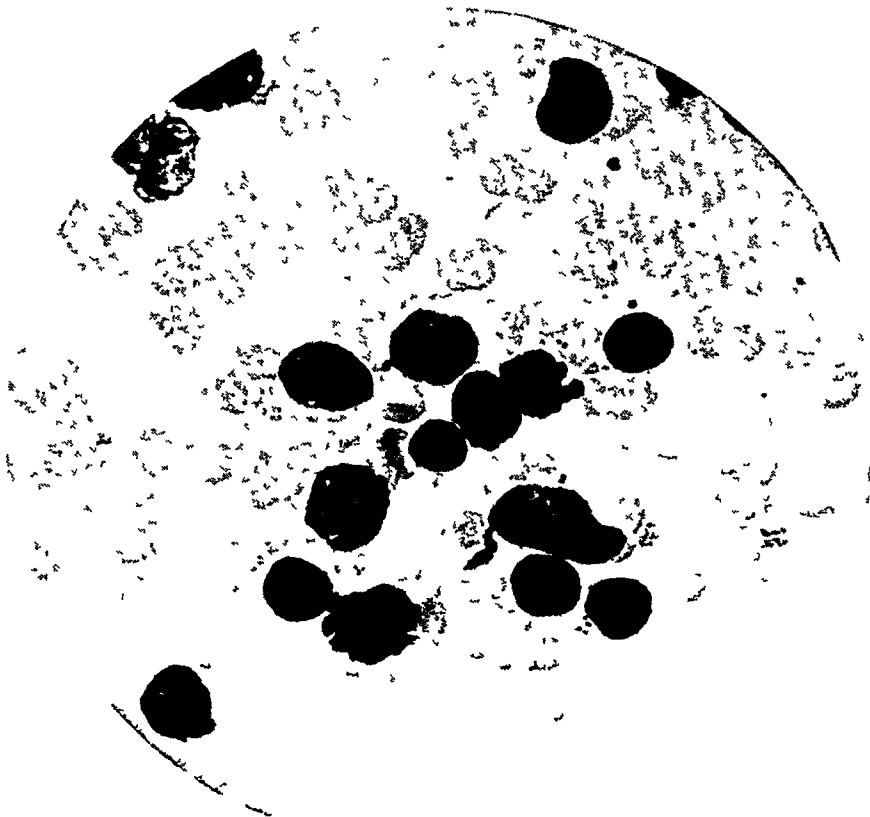


FIG 1 Stanley M, age 14 months. Splenic puncture—Normal cytology of the splenic pulp. Reticulum cells, lymphocytes, red blood cells.

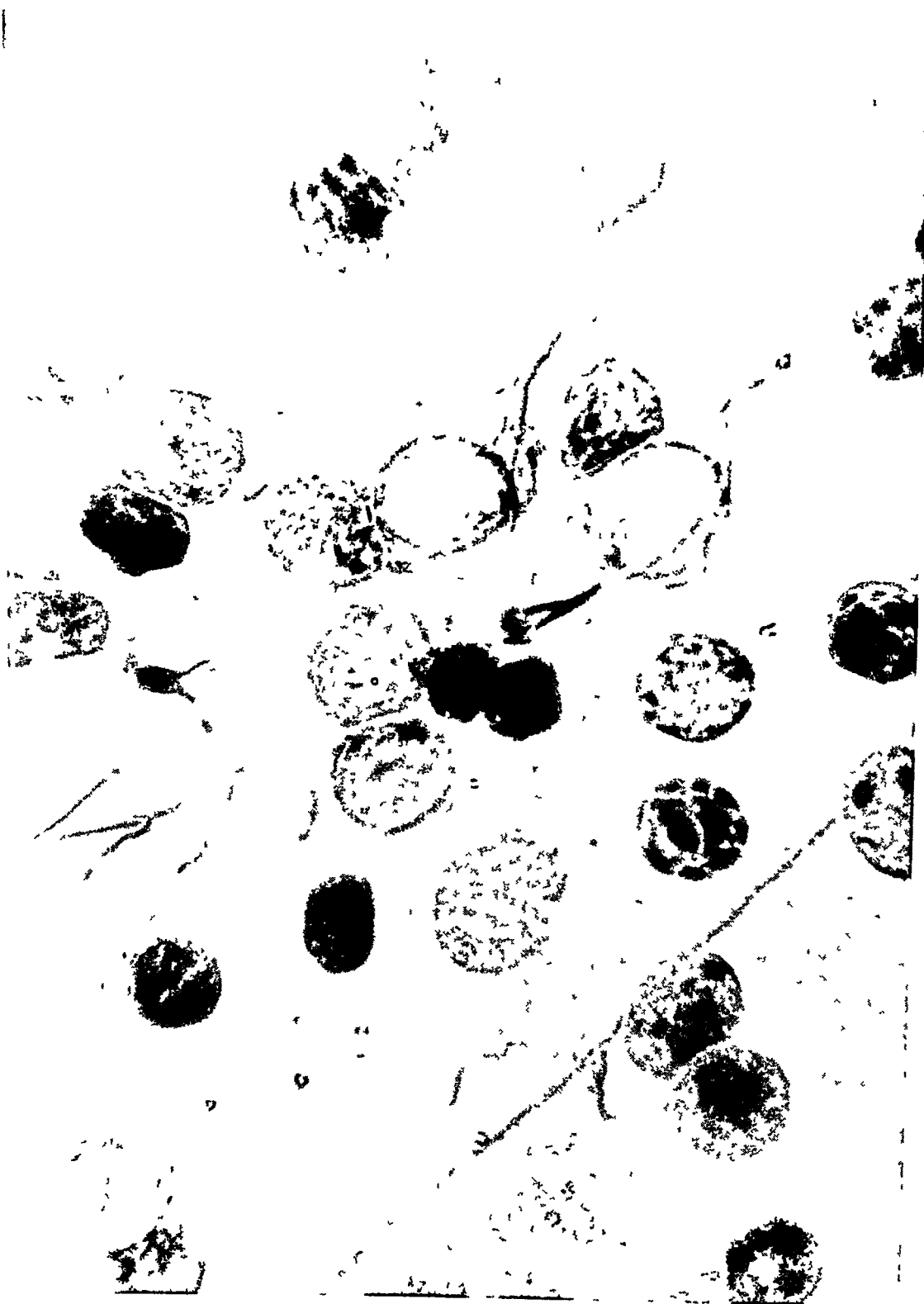


FIG. 2 Bernice M, age 18 months Splenic puncture—marked rickets with anemia and splenomegaly Normal cytology with increase in reticulum cells showing reticulum fibres and lymphocytes



ic puncture is unwarranted as clinical examination and study of the peripheral blood reveals a picture sufficiently characteristic for diagnosis

#### B Anemias secondary to defective regeneration

Under the stress of very severe chronic anemias in infancy and childhood, changes are often found in organs which, during fetal life, took part in the formation of erythrocytes. Where a marked anemia has persisted for a long time or where there has been an extensive injury to the bone marrow, post mortem studies have revealed numerous erythroblasts, myeloblasts, myelo-

cytes and other primitive cells in the splenic pulp such as are seen in actively regenerating bone marrow. Evidence of this reversion to myeloid function may be obtained by splenic puncture during life.

The nature of von Jaksch's anemia is obscure, though the majority of the investigators agree that it is closely related to secondary anemias and represents a characteristic response of the infantile hematopoietic system to stimulation rather than an independent disease. The fact that cases of von Jaksch's anemia have successfully been treated by splenectomy throws some doubt as to

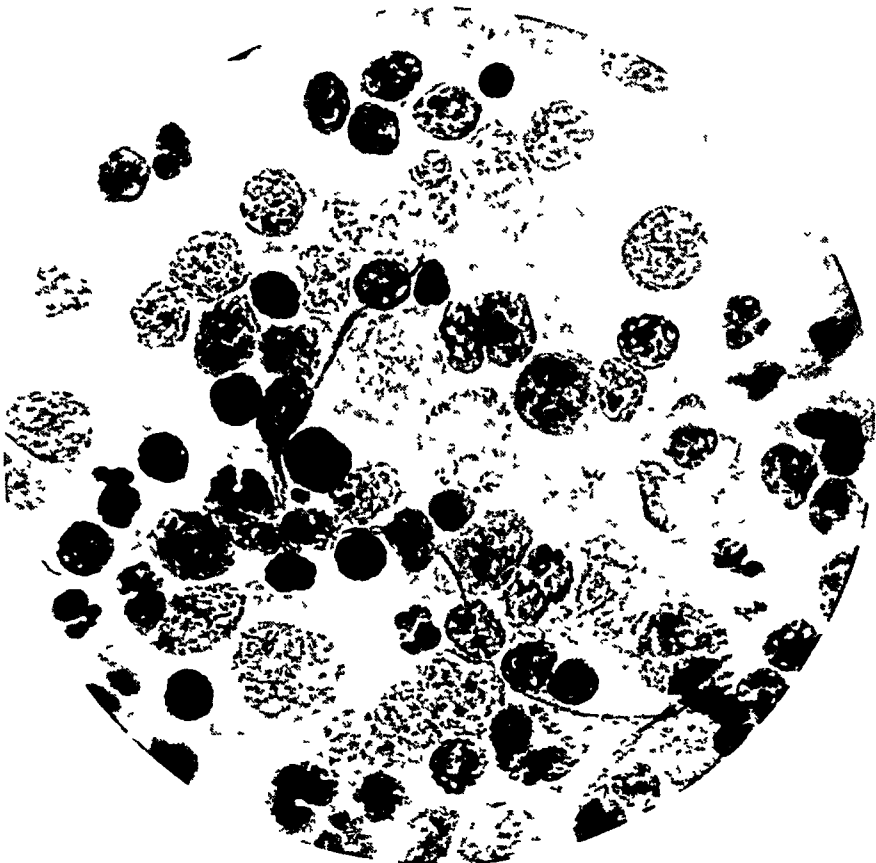


FIG 3 Thomas K, age 10 months. Splenic puncture Von Jaksch's anemia—marked myeloid metaplasia with granulocytes and red cells in all stages of development

whether the spleen itself is the seat of metaplasia in at least some of the reported cases.

### C Anemias secondary to increased blood destruction

Clinical and pathologic evidence supports the current opinion that the spleen plays an important part in the destruction of the red cell. Where this function is hyperactive one encounters splenomegaly, usually of a moderate degree.

Typical of the hemolytic anemias are

- 1 Hemolytic Icterus, congenital and acquired. Splenic puncture is not indicated as clinical and laboratory examinations will reveal the nature of the condition.
- 2 Sickle Cell Anemia, as distinguished from sicklemia (Cooley).

Reported cases of Sickle Cell Anemia show that splenomegaly is an inconstant finding (15%). It is more than likely that at some stage of the disease splenomegaly is present. In most instances even in the presence of an enlarged spleen examination of wet sealed preparations of the peripheral blood is sufficient for diagnosis. Allowing the blood to stand suspended in a physiological anticoagulant, in a sealed preparation, tends to induce the sickling phenomenon when it is not present spontaneously. It may be necessary to make repeated examinations and observe the blood for as long as 24 hours as the phenomenon is inconstant.

In the case illustrated above in Figures 4, 5, and 6, the stained

preparations of the peripheral blood showed marked erythropoiesis, reticulocytosis (40%) and monocytosis (36%). The presence of marked numbers of nucleated red cells in a child of this age would suggest von Jaksch's syndrome but the large numbers of reticulocytes and monocytes are not often associated in that condition. As none of the clinical characteristics reported in cases of Sickle Cell Anemia were found, the presence of splenomegaly in conjunction with the blood picture might have suggested a blood dyscrasia. Splenic puncture, however, established the diagnosis.

### D. Purpura Hemorrhagica

While a study of the thrombocytes in the peripheral blood, the bleeding time, coagulation time and clot retraction time gives sufficient evidence for gross diagnosis it does not differentiate the underlying pathology.

In a consideration of thrombocytopenia it is important to know whether there is an insufficient new formation of the platelets in the bone marrow due to an alteration of the stem cells of the platelets, the megakaryocytes (Wright), as seen in aplastic anemia, or, on the other hand, increased retention and destruction due to thrombocytolytic action of the spleen. It is in the latter form that splenectomy is of therapeutic benefit.

While splenic puncture might differentiate the nature of the pathologic process, the character



FIG 4 Baby W G, age 2½ years Splenic puncture Sickle Cell Anemia Fresh unstained specimen



FIG 5 Baby W G, age 2½ years Splenic puncture Sickle Cell Anemia Histiocyte with an engulfed elliptical red cell

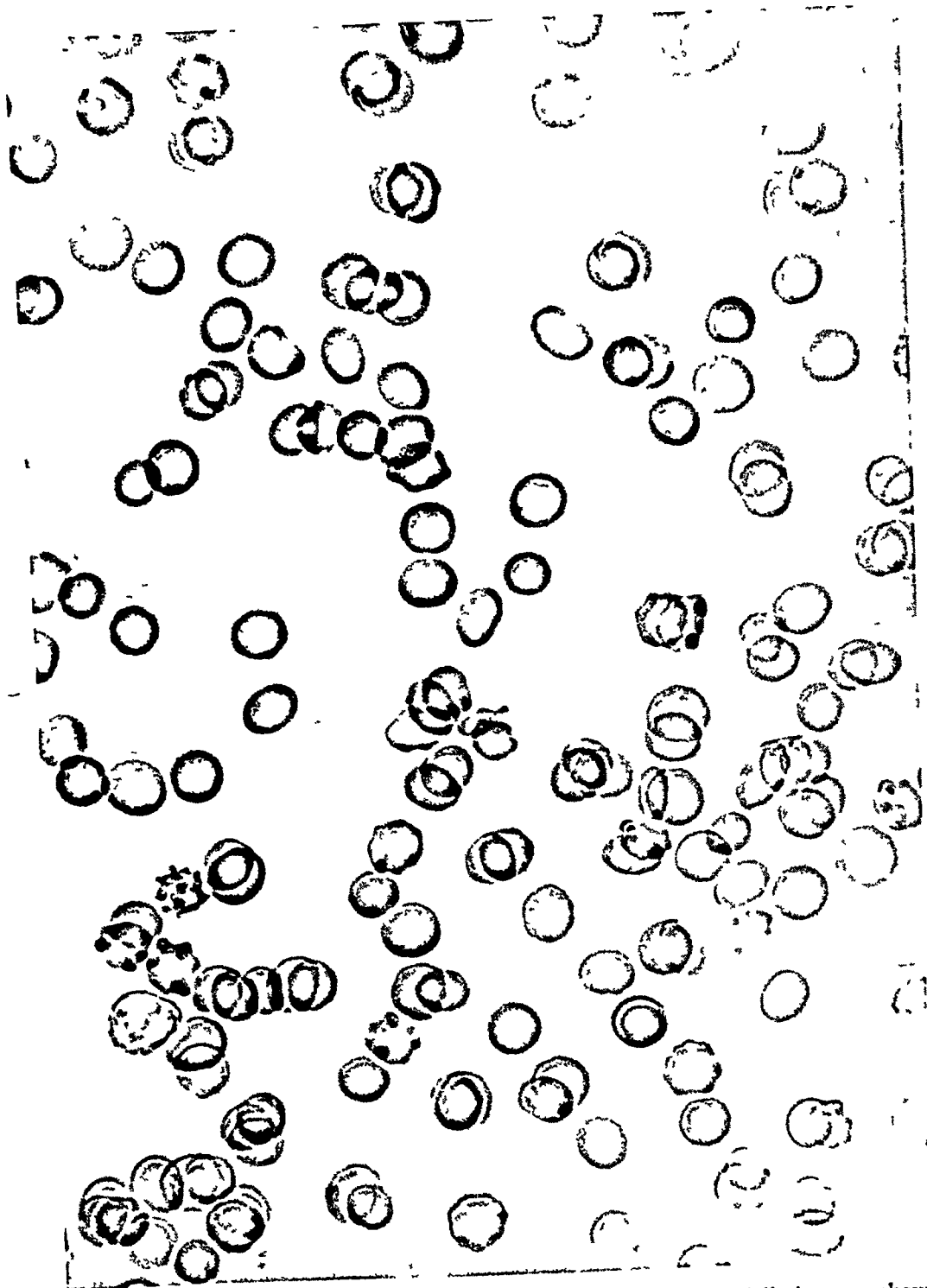


FIG 6 Baby W G, age  $2\frac{1}{2}$  years Peripheral blood Sickle Cell Anemia shows no sickle cells after having stood one hour as a wet sealed preparation

of the disease in most cases would preclude splenic puncture. This is specifically true in acute cases in which an etiologic diagnosis between purpura hemorrhagica and conditions secondary to infection has not been established.

This case made an uneventful recovery after splenectomy and one year later remains in good health.

#### E. Leukemias

In no other blood dyscrasia is the departure from the normal blood picture more striking than in typical cases of leukemia. However, much difficulty may be encountered in the aleukemic types or stages. Here splenic puncture may be of value.

Splenic puncture is contra-indicated in acute processes of leukemia when the platelet count is low.

#### II. Splenomegaly Associated with Storage Disorders of the Reticulo-Endothelial System

Even under normal conditions various lipoids may at times be stored in the reticulo-endothelial cells of the spleen. In certain cases with hypercholesterolemia and lipemia enlargement of the spleen is due to extensive proliferation of cells derived from the reticulo-endothelial system. The relationship of spleen to cholesterol metabolism was established by the work of Anitschkow, who produced infiltration of these phagocytic cells with high cholesterol feedings in rabbits.

#### A. Diabetic lipemia

In the lipemia of diabetes splenomegaly is not uncommon. The spleen becomes infiltrated with foam cells which cytologically and micro-chemically produce a picture quite similar to that of Niemann-Pick's disease. Splenic



FIG 7 Marjorie C, age 10 years Splenic puncture at operation Purpura hemorrhagica—many platelets present—megathrombocyte in process of throwing out fibrin. Blood showed only 3000 platelets per cm.

puncture is seldom indicated here as the underlying cause of this type of splenomegaly lends itself to clinical recognition

B Niemann-Pick's disease (Lipoid Histiocytosis-Bloom) (Splenomegaly-Pick)

The Niemann-Pick disease is characterized by early age of onset, its rapid course and early fatal termination. There appears to be a special predilection for the Jewish race. Many of the reported cases have shown the typical

clinical manifestations and fundus changes of amaurotic family idiocy. Mental and physical deterioration is frequently found. The skin usually presents a greyish-yellow color with the occasional occurrence of Mongolian spots.

This disease is characterized anatomically by the presence of large, so-called "foam cells". These cells are not limited in their distribution to the reticulo-endothelial system, but are also found

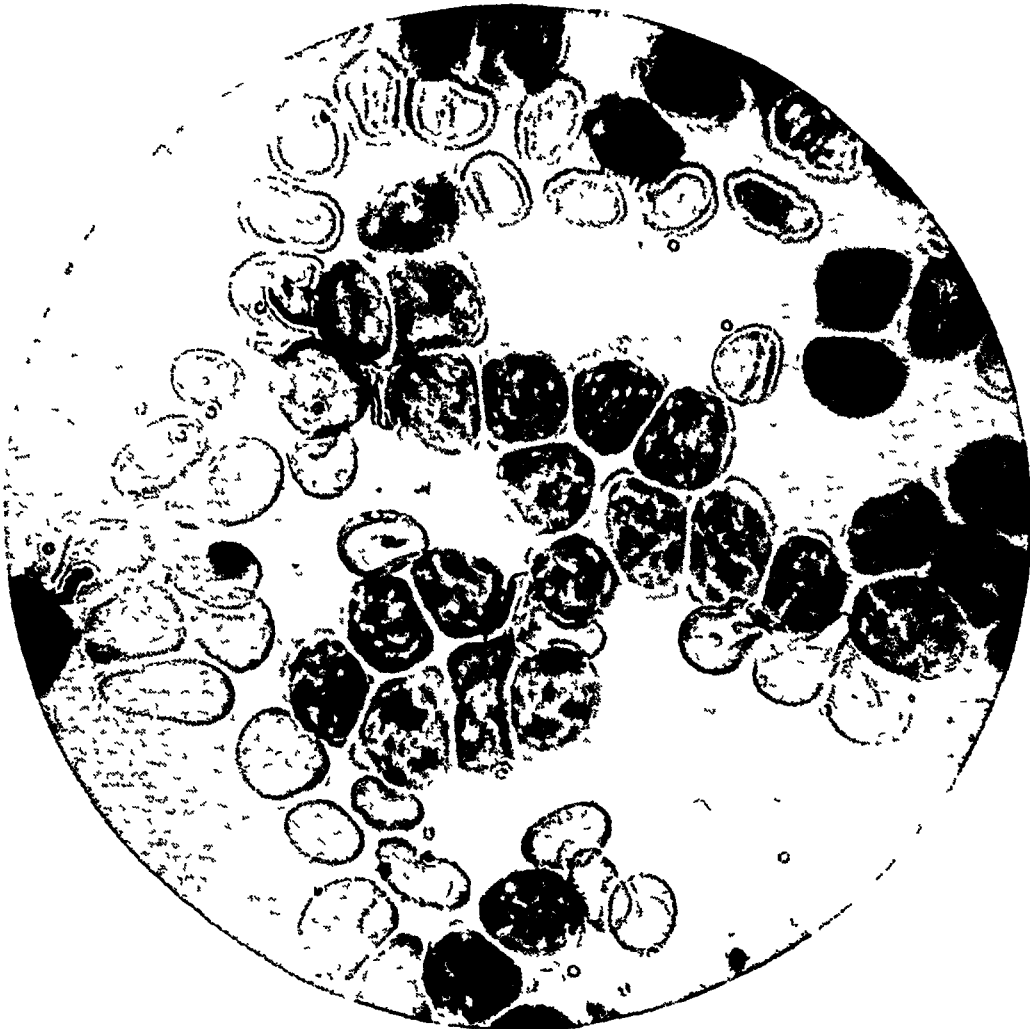


FIG 8 Splenic puncture aleukemic leukemia 800 white cells per cm of blood. Splenic puncture specimen showed more lymphocytes than red cells.

in the parenchymal cells of various organs. All organs and tissues may be involved. The spleen becomes greatly enlarged—in the reported cases it varied from 62 to 480 grams, as compared with an average normal size of 30 grams in infants between the first and second years. Pathologically, one finds the picture resulting from the extensive deposition of lipoids in the cells of the various organs.

#### C Gaucher's disease

Aside from the striking clinical differences, mainly of age and chronicity, which it shows in comparison with Niemann-Pick's

disease, it is to be differentiated anatomically from the latter in that the typical cells, except in very rare instances, are limited to the spleen, liver, lymph nodes and bone marrow. The spleen becomes enormously hypertrophied. In the spleen the sinuses, as well as the pulp are involved—in the liver the periportal connective tissue is chiefly involved—in the lymph nodes and bone marrow the changes are in the reticulum cells. Cytologically the large cell in Gaucher's disease has a characteristic longitudinal striation with Mallory's aniline blue. Many are multinuclear with the nuclei eccentrically situated.

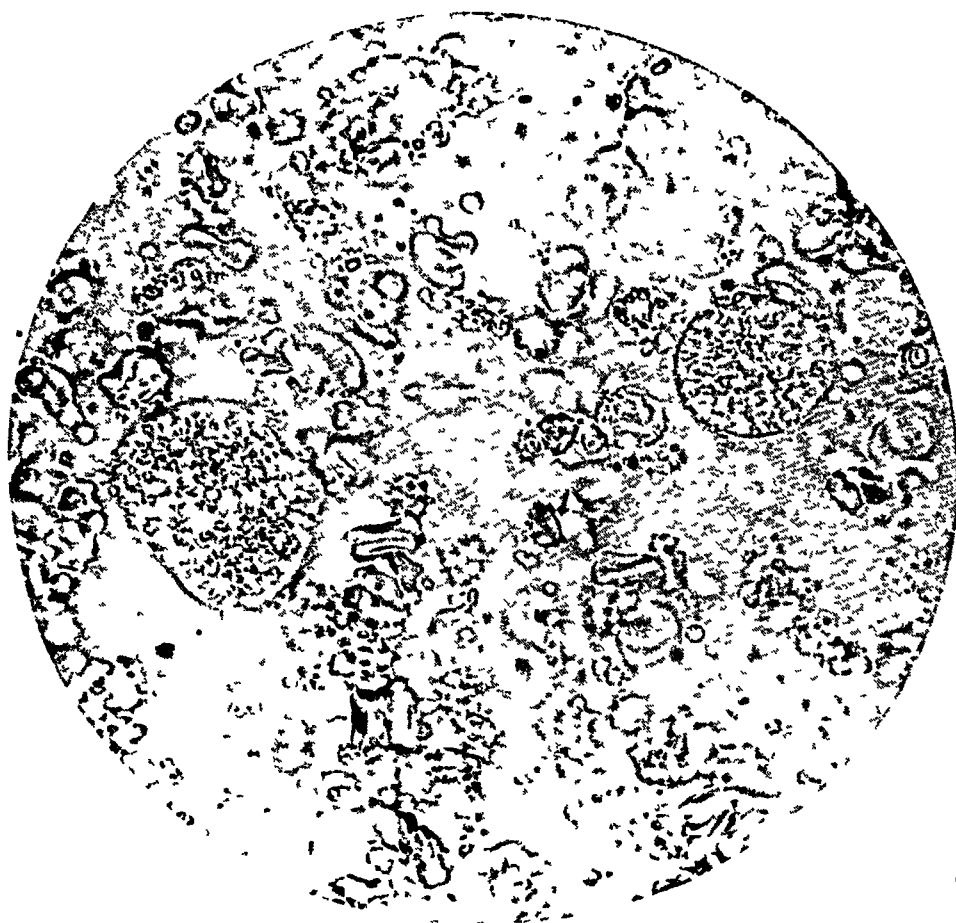


FIG 9 Alfred S, age 11 months. Splenic puncture Niemann-Pick's disease—showing histiocytes infiltrated with lipoid material (foam cells) (X 900)



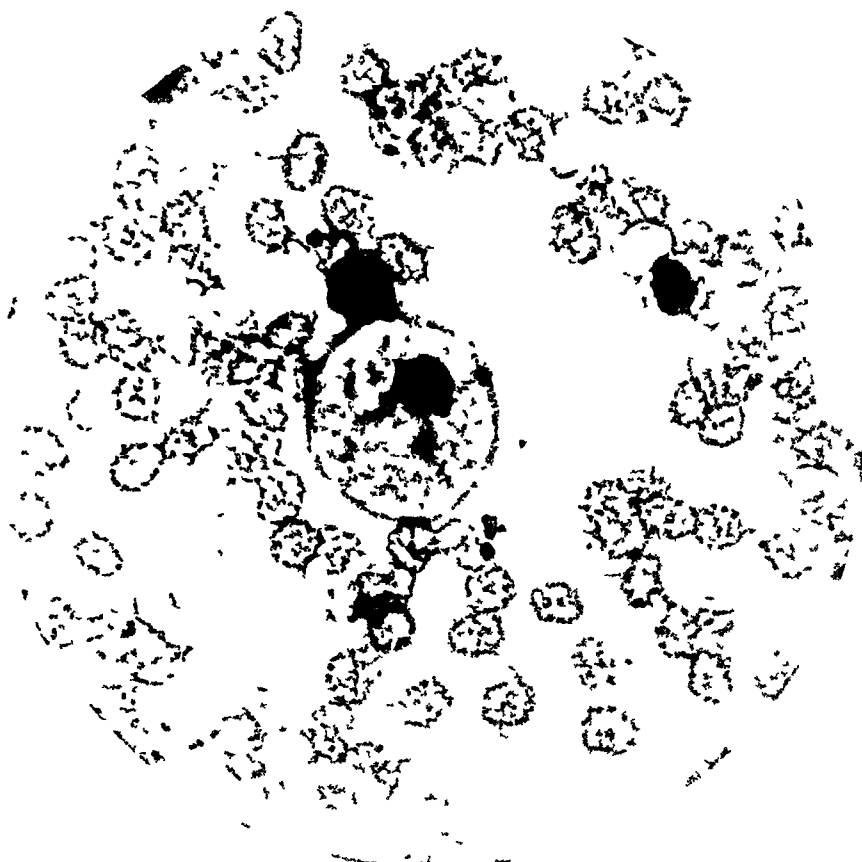


FIG 10 Alfred S, age 11 months Splenic puncture stained foam cell (X 900)

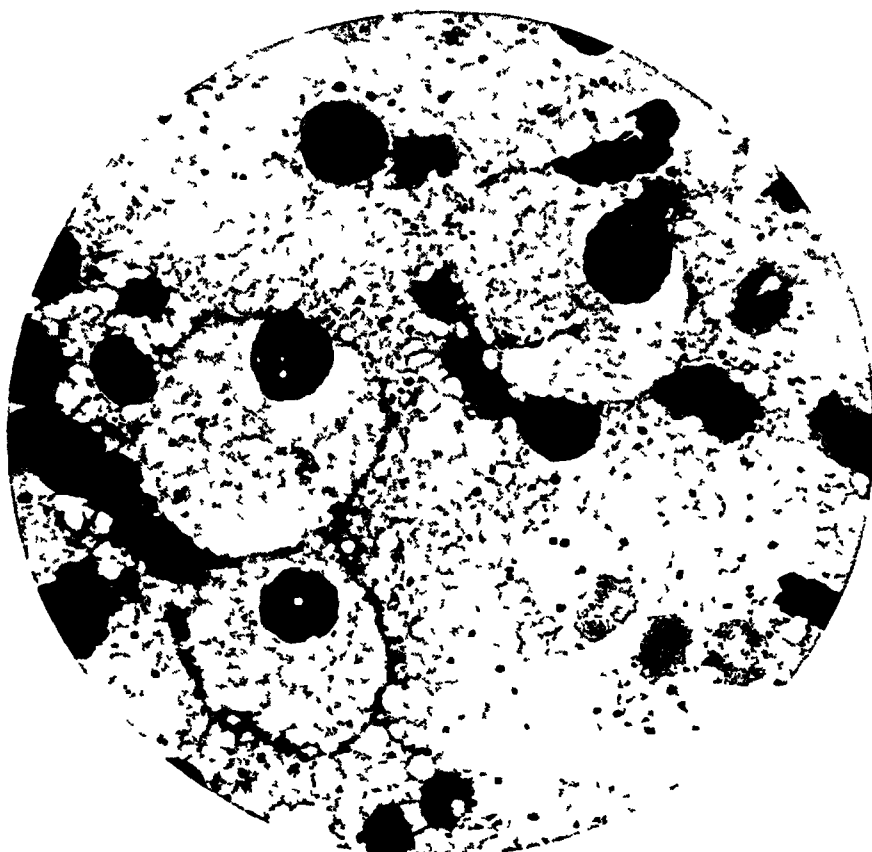


FIG 11 Alfred S, age 11 months Bone marrow puncture, showing foam cells stained (X 900)



FIG 12 Alfred S, age 11 months Peripheral blood smear showing vacuolization of a lymphocyte (X 2400)

The stored material in Gaucher's disease has been described as a complex nitrogenous substance to which the name kerosin has been applied. This according to all chemical studies is not cholesterol or lipid.

Gaucher's disease begins insidiously in infancy or childhood, usually before the thirteenth year, and pursues a very chronic course. The enlargement of the spleen, which may reach enormous proportions, is sometimes discovered accidentally or as the result of local symptoms, or else the anemia with its train of symptoms may be the first to become apparent.

### III *Splenomegaly Secondary To Bacterial and Spirochetal Infections*

Splenic puncture is only exceptionally indicated as a diagnostic procedure.

In atypical cases of tuberculosis, typhoid fever, syphilis, relapsing fever and other infections, it has been practiced without harmful results. The element of danger should, however, be given due consideration in every case.

### IV *Protozoal and Parasitic Splenomegalies*

**Malaria.** Splenic puncture, while only exceptionally necessary to a diagnosis, may be the only method by which it can be confirmed. In the absence of plasmodia the finding of histiocytes filled with the dark brown



FIG 13 Langford, age 17 months Splenic puncture—fresh unstained Gaucher's cell showing typical fibrillar appearance

granules of malaria pigment is suggestive.

**Tropical Diseases** Splenic puncture has repeatedly been used to isolate the parasites of Kala-azar and sleeping sickness

In the presence of cysts of the spleen, as seen in *ecchinococcus* infection, it should be considered as a dangerous procedure.

#### V *Tumors of the Spleen*

In hemangiomas, cysts and malignant tumors it is contra-indicated

#### SUMMARY

In summarizing, it may be stated that splenic puncture may be of value

in substantiating the diagnosis of anemias secondary to defective regeneration, such as von Jaksch's syndrome, in subacute and chronic cases of aleukemic types of myelogenous and lymphatic leukemias, Niemann-Pick's disease, Gaucher's disease and exceptional cases of bacterial and protozoal splenomegalies

Splenic puncture is contra-indicated in the symptomatic purpuras, hemophila, acute bacterial infections and in tumors of the spleen due to hemangiomas, cysts and malignant tumors. Puncture of the spleen should not be attempted in any case where the bleeding or clotting time is prolonged



FIG 14 Langford, age 17 months Splenic puncture—stained preparation of Gaucher's cell showing fibrillar structure and nucleus

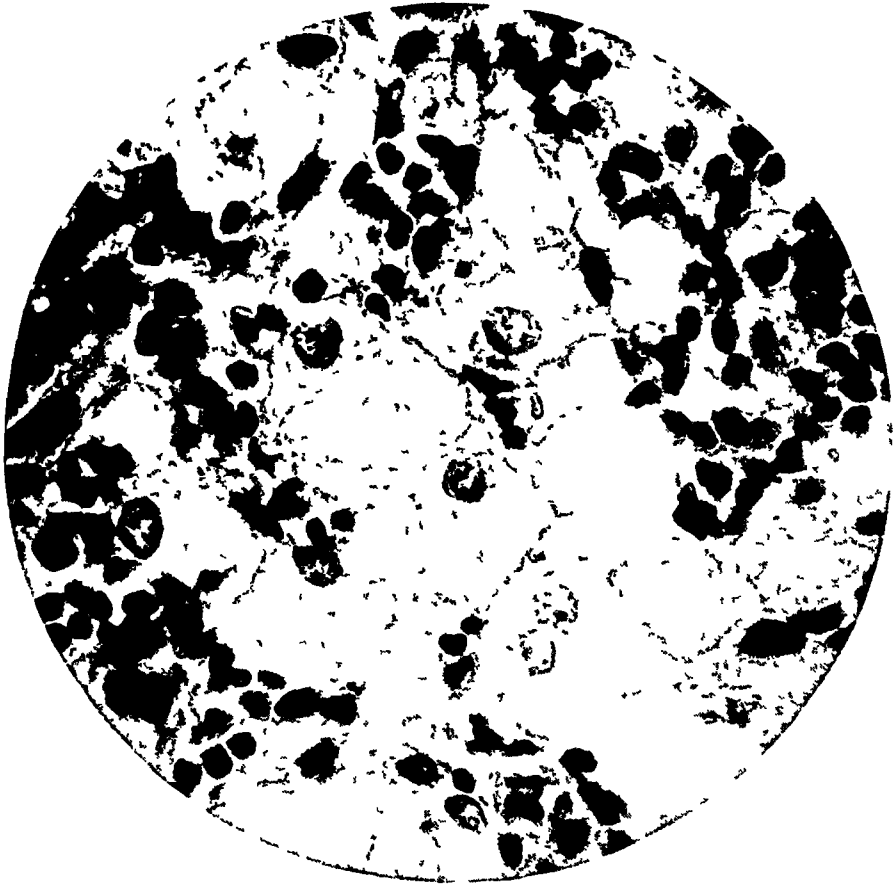


FIG 15 Langford, age 17 months Biopsy of cervical lymph gland showing typical Gaucher's cells

# Undulant Fever in California\*†

By J. EDWARD HARBINSON, M.D., *Woodland, California*

UNDULANT fever has received considerable attention in the medical literature, especially since the notable discovery by Alice Evans<sup>1</sup> of the relationship of the *Micrococcus melitensis* of Bruce to the *Bacillus abortus* of Bang. There are still many unsolved problems relative to this disease and, in our present formative stage of investigation, we should hesitate to draw conclusions from presumptive evidence.

*Incidence in United States* About 1500 cases<sup>2</sup> have been reported in the United States during the past three years. It is the opinion of the United States Public Health Service<sup>3</sup> that undulant fever is not so prevalent in this country as to constitute a major health problem.

*Incidence in California* The disease was made reportable in California in July, 1927. From this date to January, 1930, ninety-seven cases have been recorded. There is a striking difference in the number of cases listed by years. From July to December, 1927, fifteen cases were reported, the following year there were eleven, and during 1929 there were seventy-one.

The morbidity rate for 1929 in California was 159 per 100,000 population. The typhoid morbidity rate was 136 per 100,000 for the same year. The marked increase in the number of cases reported during 1929 may be explained in part by recent publicity given the disease by the medical and lay press. In addition, criteria for diagnosis of *Brucella abortus* infection are only lately being recognized by the general practitioner. As already emphasized in the literature, the incidence of undulant fever in a given community may be proportional to the efforts and earnestness of the physicians in determining its prevalence. The progressive increase in the number of cases reported in California suggests an increased incidence.

Approximately 45 per cent of the cases were reported from Los Angeles County. Possible explanations for this large percentage are available laboratory service through eleven district units of the county health service permitting a larger number of serums to be tested in suspicious cases, close proximity to Arizona, New Mexico and Texas, with possible introduction of more virulent strains of *brucella* organisms from these states, considerable medical and lay publicity in regard to the signs and symptoms of the disease.

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†From Department of Medicine, Woodland Clinic.

*Age and Sex Incidence* Two-thirds of the patients were 25 years of age or older. The greatest number were in the age group from 25 to 34. The sex incidence was fifty-nine males and thirty-eight females.

*Occupational and Regional Distribution* The occupations of the majority of the patients did not bring them in contact with livestock or with meat products. Most of them lived in towns or cities, a small percentage of them lived on farms.

*Incubation period* The onset of the disease usually was insidious, and often many incorrect preliminary diagnoses were made. The incubation period in one patient who aspirated antigen was twelve days. The usual incubation period is estimated as ten to fifteen days. The time from the onset of symptoms to the date of diagnosis varied from a few days to a year.

*Symptoms and Findings* The temperature was surprisingly high in relation to the pulse, appearance and general condition. Patients with a fever of 101 to 103 degrees had pulse rates of only 90 to 100 and respirations of 20. The pulse rate often was not over 115 with a temperature of 105.5.

The clinical findings were those which are commonly found in any type of bacteremia. The chief complaints were often misleading. One woman complained only of dysmenorrhea and nervousness. The most frequent symptoms were weakness, general malaise, fever, headache, sweats, chills or chilliness, abdominal pain and distress, anorexia, aching pains in muscles, bones or joints, weight loss of from

10 to 50 pounds, and irregularity of bowel function—usually constipation, but occasionally diarrhoea. Less frequent symptoms were nausea, vomiting, dizziness, cough, sore throat, sore gums or teeth, and catarrh. The symptoms, including fever, were usually more pronounced during the late afternoon and night. The temperature curve was more of a continuous type, with slight undulations, in most of the cases, in a few it was the typical undulatory type. It was not always possible to tell how a patient was feeling on any particular day by looking at his temperature chart as the severity of the symptoms did not always follow *pari passu* the temperature curve. One patient with a nightly temperature of 104 to 105 degrees had no chills and only very mild sweats. His only complaint was backache and he insisted on returning to work.

*Physical findings* The outstanding physical finding was an enlarged spleen. Other occasional findings were enlargement of the superficial lymph glands and enlargement of the liver. Skin manifestations varied from small crops of petechiae to erythema nodosum-like lesions. Localization of the infection gave rise to such complications as prostatitis, epididymitis, pelvic disorders, optic neuritis and cellulitis. The clinical picture was usually suggestive enough to warrant a blood test for the presence of brucella agglutinins. Most of the cases correspond to the intermittent variety of the disease. Symptoms usually disappeared after subsidence of the fever and the spleen decreased to normal size. The length of illness

varied from three weeks to eighteen months. Relapses were infrequent.

*Differential diagnosis* Undulant fever is most frequently erroneously diagnosed as typhoid, malaria, influenza, tuberculosis and arthritis, less frequently as sinusitis, endocarditis and paratyphoid. Patients may be subjected to laparotomy on account of severe abdominal pain. Certain predominant symptoms or complications may prompt the patient to consult specialists. Thus the gynecologist may be the first to see undulant fever patients for pelvic complaints, the genito-urinary specialist may be consulted for urinary complications and the orthopedist on account of joint pains.

*Atypical Cases* The atypical cases are often overlooked. One patient complained only of pruritus, and, on examination, *acarus scabiei* was found. He mentioned no other symptoms. Ordinarily this patient would have been given appropriate home treatment for this disease and his temperature probably would not have been taken. In this instance he was sent into the hospital and his temperature record showed a fever of 102. His occupation—that of milker—aroused a suspicion of undulant fever and, on questioning, he gave a suggestive history of the disease. Laboratory tests confirmed the diagnosis.

In a recent survey, a blood sample was taken from a man who had charge of an isolated herd of positive reactors. *Brucella* organisms had been isolated from the milk of these cows and recently there had been several abortions among the herd. The patient's duties included the care of the cows at these

times. He had drunk only pasteurized milk during the past one and a half years. He did not consider himself sick and probably would not have consulted a physician. He was doing his work in the usual manner. After routine questioning, we obtained a history which suggested that the infection had been present for about six weeks. His spleen was palpable and he had a fever of 102 degrees. An agglutination test was positive for *Brucella abortus* "80" in a dilution of 1:5120. *Brucella abortus bovinus* was recovered from his blood.

These are the types of cases of undulant fever which usually are overlooked.

*Laboratory tests* The average red blood cell count in this series was 4,400,000 with a hemoglobin average of 70. These figures are somewhat higher than those reported by other investigators. The white blood count varied from 3,500 to 14,500 with an average of 6,000. The polymorphonuclear average was 59 and the lymphocytes 31.

No laboratory procedure is comparable to recovery by culture of the *brucella* organisms from the blood, urine, feces, or a localized infection. Apparently the organism may remain viable in the body for years and may be recovered from the site of localization even though the agglutination test of the blood is negative.

From the patients reported from California, only three positive blood cultures were obtained. Two patients contracted their infections in the vicinity of Phoenix, Arizona, and the organisms recovered were *Brucella melitensis*. They were isolated by Dr



Karl Meyer of the Hooper Foundation We have obtained only one positive culture as already mentioned

The agglutination test is probably the next most valuable laboratory aid The procedure is essentially the same as a Widal test, except that brucella antigens are used, the strain most commonly employed being *Brucella abortus* 80 and *Brucella melitensis* 428

Most laboratories report an agglutination titer of 1:160 or higher as positive Lower positive titers excite suspicion and call for investigation by the clinician

The presence of brucella agglutinins in the blood does not necessarily imply that the individual is suffering from active undulant fever An agglutination titer of 1:1280<sup>4</sup> was found in an individual who was perfectly well and who denied any previous illness suggestive of undulant fever

Very low agglutinations of 1:15, 1:30<sup>5</sup> are found occasionally in patients with severe undulant fever A few patients with positive cultures have shown no agglutinins in their blood<sup>5</sup> It should be emphasized strongly that positive agglutination tests alone should not be considered sufficient evidence for a diagnosis of undulant fever The clinician must exercise his judgment in each case and render his diagnosis according to the mass of clinical and laboratory evidence for or against the presence of the infection It is important that all dilutions up to 1:1280 be tested on account of the pre-zone phenomena In Keefer's case<sup>6</sup> the agglutination was 1:20,000 with no agglutination up

to 1:1200 The agglutination titers in this series varied from 1:80 to 1:10,240, with an average titer of about 1:1280

In some cases agglutinins rapidly disappeared from the blood while in others relatively high titers were obtained a year or more after subsidence of symptoms Birt and Lamb<sup>7</sup> have reported the presence of agglutinins in the blood of a patient seven years after recovery from the disease

Some patients with high titers were not very sick, others with low titers had severe symptoms and vice versa Graphs of the agglutination titers were not valuable in estimating the length or severity of the illness or the prognosis

In Europe, both agglutination and complement fixation tests have been done on suspected cases The blood of one of Loeffler's<sup>8</sup> patients showed complement fixation and on agglutinins King<sup>9</sup> has been able to get complement fixation in many cases before he could demonstrate agglutinins

The skin test may prove to be a valuable diagnostic procedure Meyer<sup>10</sup> and his associates were the first to introduce this test and at present are experimenting with a purified abortus protein

Other experimenters have used both filtrates (three weeks old)<sup>11,12</sup> and heat killed suspensions of the organisms in salt solution<sup>13,14</sup> Giordano<sup>15</sup> has used the latter preparation and reports good results but rather severe reactions

The problem of bacteriological differentiations of the varieties of the brucella group is still unsettled Absorption tests, if reciprocal, are valu-

able Absorption tests on serum alone are not reliable. The dye differentiation test may be valuable but Meyer<sup>16</sup> has noted that certain dyes give contradictory results.

The guinea pig test may give valuable leads, but is not absolutely dependable. The pathogenicity tests on monkeys with recently isolated strains may classify the bovine and the porcine strains, but not the melitensis Carpenter<sup>17</sup> has recovered both typhoid bacilli and Brucella abortus from the blood of one patient, Cignini and Savorini<sup>18</sup> observed a combination of malaria and Malta fever.

During 1929, the California State Bacteriology Laboratory examined 156 blood specimens that had been sent in for the Widal test and found that five of these gave a positive agglutination with abortus antigen. It also received 164 blood specimens on which examinations for abortus agglutinins were requested. Twenty-three of these were positive, 137 were negative and four were doubtful positive (1:40 dilution).

Tests of six individuals working in one laboratory devoted almost exclusively to brucella research work showed four positive reactors. Half of the workers in another laboratory doing the same type of work showed positive agglutinins in their blood. Of all these workers, only two had definite symptoms of undulant fever. Many serums were tested for cross agglutination with Bacterium tularensis but none were found positive.

*Brucella infections as a cause of abortion in women* We have tested the serums of twenty-five women who have repeatedly aborted. The agglu-

Carpenter<sup>19</sup> examined blood samples from twenty-eight women who aborted and made bacteriological studies on twenty-seven fetuses and twenty-eight placentas. In thirteen cases the placenta and fetus were from the same case, making forty-two abortions from which material was examined. Abortions ranged from thirty days to the seventh month of pregnancy. There was no evidence that Brucella abortus was the cause of the interrupted pregnancies. Simpson<sup>20</sup> reports an agglutination titer range from 1:80 to 1:329 for five women who repeatedly aborted. Four of these women gave history of a previous febrile illness. All consumed raw milk.

Cornell<sup>21</sup> examined the serums of 1015 women reporting to the prenatal clinics of Chicago Lying-in and Cook County Hospitals. Five serums gave weakly positive reactions. None of these patients gave any suggestive history of undulant fever and, clinically, there were no premature interruptions of pregnancies. Two of the patients were delivered of normal children at full term. Twenty-three cases of abortions in women were studied. Twenty-two patients were negative and one gave a weakly positive reaction with placental blood. The venous blood was negative.

Kristensen<sup>22</sup> isolated Brucella abortus from the exudate which covered the uterine site of the placenta in a seven months fetus. No organisms

were isolated from the stomach, intestine, lungs, liver, spleen or kidneys of the fetus

Frei<sup>23</sup> isolated brucella organisms from the vaginal discharge of a woman ten days after the onset of symptoms

#### *Treatment of Undulant Fever*

Many types of treatment have been used, but, in our experience, none has been so uniformly successful as vaccine. The best results have been obtained when the dosage was sufficiently large to produce a febrile reaction of 2 to 4 degrees. We have used a sensitized mono-bacterial vaccine prepared from a human abortus strain. The initial injection was  $\frac{1}{4}$  cc. Injections were given every day, doubling the amount of vaccine given on each occasion. Suitable febrile reactions usually were obtained with 1 to 2 cc of the vaccine. Vaccine contained 1,000,000,000 organisms per cc.

*Deaths* There were two deaths among the ninety-seven patients reported in this series. One of them had suffered from endocarditis and myocarditis for many years prior to the onset of undulant fever. He did not have the malignant type of the disease. A post mortem examination of this patient was permitted and the following findings recorded:

Numerous petchiae on the back and scattered over the upper arms and chest.

*Lungs* Broncho-pneumonia, chronic passive congestion all lobes of both lungs, hemorrhagic tracheo-bronchitis and lymphadenitis.

*Heart* Weighed 420 grams, marked hypertrophy of right ventricle, large vegetation present on the mitral valve,

extending onto the under surface of the aortic cusp.

*Spleen* Weighed 470 grams, large and flabby, cut surface light red.

*Liver* Weight, 2,725 grams, capsule smooth, but with a mottled appearance, cut surface showed chronic passive congestion with patches of marked parenchymatous degeneration.

*Gastrointestinal Tract* Upper part of esophagus and larynx congested, vessels prominent, but no bleeding points found, stomach mucosa somewhat congested, no pathological change found in small or large intestine.

*MICROSCOPIC EXAMINATION Heart* Several masses of perivascular exudate consisting of large mononuclears, lymphocytes and a few polymorphonuclears.

*Tracheal Lymph Node* Congested, sinuses filled with blood and exudate, number of polymorphonuclears, endothelial cells, some edema and hazing of architecture.

*Bronchial Lymph Node* Same picture, but exudate was more mononuclear.

*Testicle* Not remarkable.

*Spleen* Capsule slightly fibrosed, considerable blood in pulp, splotches of hyalin in follicles, which looked like amyloid, media of the follicular arteries also showed considerable of this material, pulp showed marked hyperplasia polymorphonuclears.

*Liver* Marked central congestion with almost complete destruction of central parenchymal cells and invasion of polymorphonuclears, considerable fat in remaining liver cells, in small droplets, occasional excess of exudate in periportal tissue, mostly small mono-

nuclei, few large polymorphonuclears

Methylene blue stains of lung and lymph nodes failed to reveal any gram negative bacteria

Cultures were made from heart blood and spleen on blood agar plates and in broth

Guinea pigs were inoculated with splenic material but showed no effects in ten weeks. Serum from the guinea pigs did not agglutinate *Brucella melitensis*

Postmortem examinations<sup>24,25</sup> on several patients dying of undulant fever in the United States have shown vegetative endocarditis. *Brucella* organisms have not been demonstrated in the vegetations on the valves in any of these cases. In most instances it may be assumed that the toxemia incident to undulant fever is responsible for the exacerbation of the endocarditis and that the patient's death is due to cardiac failure rather than endocarditis caused by *brucella* organisms

*Source of Infection* Our knowledge of the source of infection in undulant fever is still very limited. Carpenter<sup>26</sup> and others have presented considerable presumptive evidence to show that raw milk from infected cows is one of the principal sources of infection. Nearly all of the patients in this series drank raw milk. It is said that Los Angeles County, which has the highest county morbidity for undulant fever in California, uses more raw milk than any county in the United States. There are 700 raw milk producers in this county, the number of cows in each dairy varying from two to ten or more. Eighty per cent of the supply to Los Angeles City is pasteurized, and 65

per cent of the supply outside the city is pasteurized. It is a question whether the facts shown by these statistics may have some bearing on the large number of cases reported from this county. In one dairy of seventy-two cows 38 per cent were positive reactors

The first test of 4,000 head of cows in certified dairies showed 37.5 per cent of positive reactors. In order to replace the positive reactors, a large number of cows were tested at various purchase points in the United States. Thirty per cent of these cows were positive reactors

Five thousand and fifty-five blood specimens were received by the University of California Farm for the agglutination test for Bang's disease of cattle during the year ending June 30, 1929. The specimens were from scattered areas throughout the state and from 121 herds of ten animals or more. Sixty-two per cent of the specimens were positive. The general State average of positive reactors is conservatively estimated as 40 per cent to 50 per cent

Coolidge,<sup>27</sup> Carpenter,<sup>5</sup> and Frei,<sup>23</sup> individually, have given infected milk to several volunteers, but no clinical symptoms of undulant fever were produced. Gabbi<sup>28</sup> and Otero<sup>29</sup> have recently been successful in infecting individuals by this means

We are unable to explain the low incidence of undulant fever in children, the principal milk consumers. It has been shown that *brucella* infection in calves disappears soon after discontinuing feeding infected milk. Perhaps there is a greater natural immunity before puberty, which progres-

sively decreases with the establishment of the sexual function

There are several goat dairies in California, distributing raw milk. Goat's milk was not a source of infection in any of the patients who contracted their infection in California.

The evidence is fairly conclusive that several patients have contracted their infection by contact with live stock or animal products. We examined the blood of sixty veterinarians and found positive brucella agglutinins in six. In one the titer was 1-40, in two 1-80, in two 1-160, and in one 1-320. Four of the men drank only pasteurized milk. All of these men gave histories suggestive of undulant fever. Several with negative agglutination titers also had had pyrexia of unknown etiology. The incidence of abortus antibodies in the serums of these individuals is much higher than that generally reported for human serums.

In California undulant fever has been recognized as an occupational disease. In most instances there was considerable evidence to show that the brucella infection had been acquired either by accidental inoculation while at work or by contact with infected animals or animal products.

"Cornell"<sup>21</sup> has suggested the possibility of poorly cooked liver or meat as a source of infection. Other animal glandular products may be included also.

Several attempts<sup>30,31,32,33</sup> have been made to infect humans by injections of live organisms, but all have been unsuccessful. We have sufficient proof in the numerous laboratory infections reported, that inoculation with human

abortus strains may take place through abrasions or injections.

*Incidence in Animals* We are commencing to learn about the prevalence of this infection among the phyla of the animal kingdom. Emmel and Huddleson<sup>34</sup> have recently described *Brucella abortus* infection in chickens. Abortus organisms have been isolated from fistulae of horses<sup>35</sup> and it is believed that *Brucella abortus* is associated rather closely with poll-evil and fistulae. We examined the blood serum of a cat fed infected milk since birth, but found no brucella agglutinins.

Many sources of infection besides those already considered may be revealed by further study. We need more accurate and definite information regarding the source of infection in man. In the mean time, as considerable evidence has accumulated incriminating raw milk as a source of infection, it would seem best that ordinary raw milk be pasteurized before consumption, as a prophylactic measure. Certified milk is safe if regular periodic tests show no positive reactors in the herds.

It is possible to free herds from infection as shows by the records of several of the certified dairy herds in California. In this state certified milk bearing a cap with the seal of the American Association of Medical Milk Commissioners, comes from cows which react negatively to the agglutination test for *Brucella abortus*.

Traum<sup>36</sup> and Carpenter<sup>37</sup> pointed out that, on rare occasions, brucella organisms may be eliminated in the milk of non-reacting cows. Of three cows which were eliminating brucella

organisms, though their serums were negative, Traum found that one soon became a positive reactor and the other two ceased to eliminate the organisms. He feels that, even though such an animal exists in the herd without detection, the high dilution of the milk from this cow by the rest of the milk from a large dairy, practically frees it from the danger of transmitting infection.

Extreme care should be exercised in

the handling of animal fetuses as infection in at least two of the cases reported from California have been traced fairly definitely to this source. Contact with livestock seemed to be a source of infection in a few instances.

NOTE: Dr Harbinson was taken ill during the Minneapolis meeting. His death took place one week later (Editor).

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# "Polymorphonuclear Leucopenia" A Proposed Classification

By J SHIRLEY SWEENEY, M D , Sc D , F A C P , *Dallas, Texas*

**A**GRANULOCYTOSIS was first reported by Schultz in 1922. In the last seven years, many observers have added cases. The number has amounted now to nearly one hundred cases<sup>1</sup>. When one reviews the literature on this disease, he is impressed with its protean manifestations. Blumer<sup>2</sup> has recently drawn attention to the fact that all cases do not conform to Schultz' original description. One finds cases without anginal lesions, with anemia, with only moderate reduction of white cells, etc. The natural inference is, therefore, that agranulocytosis as an entity has not been completely described.

Much has been written in an effort to define the etiological mechanism and symptomatology of this condition. Rose and Houser<sup>3</sup> consider it a non-specific infectious condition. Farley<sup>4</sup> has called attention to the blood picture following arsenical poisoning which follows closely that described for agranulocytic angina. Such cases do not show necessarily any signs of angina. The symptom complex, including high temperature, seems to be a result purely of a chemical intoxication. This is interesting in so far as it excludes any bacterial participation. Farley<sup>4</sup> lays great stress in such cases on the inhibiting effect of arsenic

on the bone marrow. I have observed two cases, in which there was a definite agranulocytosis with hectic symptoms following the administration of neoarsphenamine.

Gordon<sup>5</sup> has recently reported four cases under the term "agranulocytosis". He appends a very excellent bibliography. In this article, as in many others on this subject, there is considerable uncertainty and speculation regarding the proper name of this condition. One finds different terms applied—agranulocytic angina, agranulocytosis, malignant neutropenia, etc. The same confusion is found as regards the etiology. There is even some doubt as to whether this condition is a disease entity. The symptomatology is likewise not clearly defined and in the list of therapeutic suggestions one finds much to choose from. There seems at the present only one really constant and universally accepted finding—a polymorphonuclear leucopenia. Even the presence of membranous ulceration is not constant if one accepts all the reports of cases under the term agranulocytosis. There is likewise no distinctive pathological picture of this condition.

Because of this confusing etiological, symptomatological and pathological variability, it is exceedingly desir-



able that there should be some clinical classification, which would be at least a first step in the proper understanding of this disease process and in removing it from its present state of chaos

Using the one constant finding of the condition as a starting point, the following etiological classification is suggested: 1. Infectious polymorphonuclear leucopenia; 2 Toxic or chemical polymorphonuclear leucopenia, 3 Symptomatic polymorphonuclear leucopenia; 4. Idiopathic polymorphonuclear leucopenia.

In the first group are included those conditions that begin with symptoms of an acute upper respiratory infection, high fever, chills, sore throat, etc., without a history of arsenical medication. Within a variable period, from one to two days, there develops painful swallowing, an ulcerative stomatitis which soon becomes gangrenous, swelling of the neck, malaise, severe toxemia and prostration. Other symptoms are variable. There may develop ulcerations of the vaginal or rectal mucosa, sometimes very extensive and severe. In some patients icterus appears. The liver and spleen may enlarge and there may be a general glandular enlargement. The toxemia increases, delirium supervenes and death usually follows. The course of the disease is usually acute and rapidly fatal, seldom lasting over two weeks, without recovery. Early in the course of the illness, the blood count may be normal. The red cells may or may not be effected. The white cells soon show a decrease and drop very rapidly to complete disappearance if the disease proves fatal.

The granular cells are the elements that disappear and there results a relative increase in lymphocytes.

In the second group are included those cases that follow the administration of some chemical, principally the arsenical preparations. Radium poisoning produces practically the same pathological picture. Recently, there have appeared in the literature several articles calling attention to the potential dangers inherent in the administration of arsenical compounds. Most recently Farley<sup>4</sup> reports several of such cases. It is more difficult to outline the onset and development of symptoms in this form of polymorphonuclear leucopenia than that described in the foregoing paragraph. The reason is that the individual susceptibility to arsenic varies so much. Some patients show a marked dermatitis, high temperature, malaise with a polymorphonuclear leucopenia of varying degrees, etc., following a single injection of arsenic. Other patients will manifest symptoms only after a large series of such injections. Likewise, in some there are ulcerative or gangrenous lesions present, while in others such signs never appear. It would seem that the presence or absence of these membranous ulcerations depends on the rate and degree of the disappearance of granulocytes from the blood stream.

In the infectious type it is not clear whether the ulcerative lesions precede or follow the reduction of white cells. There are numerous cases reported of this form in the early stages of which the white cells are normal. At the same time, there are what seem to be unquestionable cases of the toxic form

that begin with severe ulcerative lesions in the mouth or throat. The exact relationship, therefore, between the time of ulceration and decrease in the polymorphonuclear leucocytes is not always clear. One finds in the literature a diversity of thought regarding this phenomenon. It has been suggested by some that the ulcerations are dependent upon the disappearance of the polymorphonuclear leucocytes, while others are inclined to consider the polymorphonuclear leucopenia the result of the membranous ulcerations. It is conceivable that there might be a qualitative change in the granulocytes that could account for the loss of local resistance and subsequent ulcerations before a quantitative change in them is demonstrable.

In the toxic or chemical group, dryness in the pharynx, which is often the first symptom, followed by intense congestion and frequently extravasation of blood into the tissues with necrosis or sloughing in which very little odor is noticeable, characterizes the progressive changes. The cervical glands usually become swollen, thus giving the characteristic swelling of the neck. All of these symptoms may or may not be associated with skin manifestations. From my own observations I am inclined to believe that frank ulcerations or gangrenous lesions do not occur without a material diminution of the polymorphonuclear leucocytes.

The clinical picture, therefore, of a rather severe malaise and prostration, fairly high temperature (102 to 105 degrees) with or without gastrointestinal upset, often associated with a diffuse erythematous dermatitis, frequently involving the mucous mem-

brane, with or without frank ulcerations, coming after or in the course of arsenical medication principally, and accompanied by a gradual decreasing white cell count—polymorphonuclear leucopenia—should be considered until proved otherwise that of a toxic or chemical polymorphonuclear leucopenia.

The mortality in this type does not seem to be as high as in the infectious form. The variable would appear to be the susceptibility of the hemopoietic system and its recuperative power.

The group, symptomatic polymorphonuclear leucopenia, would include those conditions in which such a blood picture is found and is of such a degree as to be considered a determinant in the course or prognosis of the primary disease. Such a classification is not designed to change the name of the primary process but to avoid confusion in terminology and diagnosis. For example, one finds in the more severe pernicious anemias a polymorphonuclear leucopenia, which is a symptomatic manifestation, but differential diagnosis can be made. Likewise, in some of the leukemias, notably the so called aleukemic leukemia, which is diagnosable by careful blood studies, one may find definite polymorphonuclear leucopenia. The same may be said of the secondary or aplastic anemias, such as occur in benzol poisoning and the severe streptococcal blood stream infections. The recognition of the granulocytic picture in such conditions as a symptomatic process would help a great deal in avoiding diagnostic confusion.

Finally, in the group, idiopathic polymorphonuclear leucopenia, would be included those cases the etiology and nature of which are so obscure as to prevent their inclusion in one of the other three groups

As stated in the beginning, the classification that has been suggested is intended purely as a clinical one. There is no constant bacteriological, symptomalogical or pathological picture of "agranulocytosis" or polymorphonuclear leucopenia. By combining the mode of onset and etiological information, one can, by the classification offered herein, at least acquire a convenient working differentiation of this very interesting disease process. By

using such a classification, the morbidity statistics of this condition may begin to mean something. As it is, they are just a heterogeneous mixture of pathological states manifesting a polymorphonuclear leucopenia.

#### SUMMARY

A clinical classification of the states exhibiting a polymorphonuclear leucopenia has been outlined. The classification is based on the mode of onset and the etiology and is: 1 Infectious polymorphonuclear leucopenia; 2 Toxic or chemical polymorphonuclear leucopenia; 3 Symptomatic polymorphonuclear leucopenia; and 4 Idiopathic polymorphonuclear leucopenia.

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# Proctosigmoidoscopy: A Medical Diagnostic Procedure\*

## A Plea for a Wider and More Frequent Use of This Method by the Internist.

By MOSES PAULSON, B S., M. D., F.A C P., *Instructor in Clinical Medicine,  
Johns Hopkins University, Baltimore*

THE proctosigmoidoscope brought into being the surgical specialty of proctology much the same as the stomach tube gave birth to gastroenterology and the electrocardiograph to cardiology. As a result, sigmoidoscopy became a surgical procedure, an instrument to be used mainly by proctologists and general surgeons. The method, in its earlier days was, and in many places still is, attended by preparation which rivals that of a major surgical procedure. Indeed, even at this late day it is not uncommon to note the posting of proctoscopic examinations upon the operating room schedules of many of our large hospitals. This state of affairs has passed from one medical generation to another and as a result few internists employ proctosigmoidoscopy as a diagnostic procedure. It is felt that this is a mistake, that proctosigmoidoscopy is an essential medical diagnostic procedure to be used by internists because of the very nature of the conditions in

which its employment is indicated. It is to call attention to these facts that this paper is written. Diagnosis, in the main, is a medical problem. If it only were possible to offer this very general and obvious fact as a reason for the use of proctosigmoidoscopy by the internist, it would appear that this alone would be sufficient to place the procedure in the same category as that of other endoscopic methods in general usage such as ophthalmoscopy, laryngoscopy, sinus transillumination, otoscopy and the like.

Concretely, however, the reasons for the necessity of the employment of the proctosigmoidoscope by the internist as a diagnostic method, are more cogent. It is felt that an examination is incomplete without submitting the patient to proctosigmoidoscopy when there is a history suggesting even the slightest deviation from the usual bowel habits. Besides, usually cases are seen first by the internist, and if there be any virtue in the establishment of early diagnoses, then many opportunities for so doing are lost if one waits until manifestations become more pronounced or until the patient

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\*From the Department of Medicine, Gastro-Intestinal Clinic, The Johns Hopkins Hospital and University School of Medicine, Baltimore

reaches the proctologist or surgeon at a later date. Also, many of the problems encountered within the intestine are primarily medical in nature. Take the question of the colitides! These conditions are medical essentially; they become surgical secondarily upon the failure of proper medical management after a reasonable trial, or upon the arising of complications which call for surgical intervention, or upon manifestations which are growing worse that cannot be controlled by medical means. Obviously, the use of the proctosigmoidoscope by the internist is essential here. To attempt to study, diagnose and manage these problems without proctosigmoidoscopy would appear in the same light as investigating and treating a complaint of sore throat without ever having inspected the mouth and pharynx. Also, the topical application of medicaments in localized conditions within the rectum or sigmoid through the sigmoidoscope is, in our opinion, not outside of the province of the internist. Even in cases of "Irritable Colon", the functionally disordered bowel, proctosigmoidoscopy by the internist is indicated, for the problem is purely medical in nature. Further, those conditions recognized as surgical from the standpoint of treatment—hemorrhoids, polypi, malignancy, fistulae, etc.—are of as much concern to internists as to proctologists and surgeons, for these cases usually are seen first by internists, and since early and correct diagnosis here is essential too, proctosigmoidoscopy should be employed by the physician to accomplish this satisfactorily.

The importance of proctosigmoidoscopy by the internist will be appreciated further, when it is realized that most of the intestinal involvements, functional and organic, evidence their earliest manifestations in the rectum and lower sigmoid and consequently are within reach of the instrument; and also that the roentgen-ray as a method of diagnosis in colonic disorders, is least satisfactory in rectal and lower sigmoidal conditions.

In recent years, the proctosigmoidoscope has assumed other usages which are purely medical in nature. The securing of material for bacteriological study directly from the suspected or involved rectum or sigmoid through a proctosigmoidoscope has been found superior to that obtained from defecated feces, for when the material is obtained through the instrument it is fresh and is procured directly from the site desired. Methods have been devised and elsewhere described of securing material for bacteriological examinations directly from the rectum or sigmoid from the exact point desired through a sigmoidoscope without contamination from surrounding sources or by the instrument<sup>1</sup>. Incidentally, this procedure was originally employed in our bacteriological studies with regard to etiology in chronic ulcerative colitis<sup>2</sup>. In addition, it has been demonstrated that diagnosis of human intestinal protozoa can be improved about 350% by studying dejecta secured directly from the sigmoid through a sigmoidoscope than by an examination of defecated feces<sup>3</sup>. These are medical problems pure and simple in which the use of the proctosigmoidoscope by the internist is a pre-

requisite to the proper application of these newer methods.

At Johns Hopkins, proctosigmoidoscopy has been practiced for some years as a medical diagnostic procedure on the medical wards and in the Gastro-Intestinal Clinic members of the staff employ this method when indications arise. The instrument is inserted from 20 to 30 cms., without the aid of any type of anesthesia, narcotic or sedative, and the glamor as well as the elaborateness still attending this method of diagnosis in some places, has been removed.

Students are being given the medical point of view regarding proctosigmoidoscopy and intestinal disorders. To this end, life-like and life-sized models of conditions in the rectum and sigmoid as seen through a proctosigmoidoscope have been devised for individual and group instruction thus enabling either the presentation of the entire gamut of lower bowel disorders almost simultaneously, or the demon-

stration of a particular condition in the absence of a suitable case<sup>4</sup>.

In view of the foregoing, it is urged that proctosigmoidoscopy be regarded as a medical diagnostic procedure, that it assume a position in the hands of the internist similar to that of such methods as ophthalmoscopy, otoscopy, laryngoscopy, sinus transillumination and the like, and that students be taught this point of view.

#### SUMMARY

Proctosigmoidoscopy has been urged as a medical diagnostic procedure, a method to be used by internists like ophthalmoscopy, to facilitate the problem of early diagnosis in intestinal manifestations; and also because the very conditions in which proctosigmoidoscopy is employed, are, in many instances, medical problems essentially, or are, in other instances, at least of as great importance to physicians as to surgeons and proctologists.

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## Editorial

### *HEPATIC LESIONS ASSOCIATED WITH EXOPHTHALMIC GOITER*

For a number of years we have noted that the livers of patients dying with exophthalmic goiter in the University Hospital presented significant pathologic changes. Many showed some degree of simple or pigment atrophy, but the most common and striking hepatic change was the very frequent occurrence of a marked diffuse fatty degenerative infiltration, bearing all the earmarks of a severe toxic process. In a number of cases this lesion has been so marked as to call forth comparisons with the classical phosphorus liver. To make the resemblance to the latter condition more close, the hearts and kidneys of the same patients presented a marked fatty degenerative infiltration. In one patient, a young girl of seventeen, who died of fulminating exophthalmic goiter symptoms of only twenty-four hours duration, these pathologic lesions were so marked as actually to cause a suspicion of phosphorus poisoning. In cases of exophthalmic goiter in which death occurred after operation and anesthesia, it is impossible to attach direct importance to the presence of an acute fatty degenerative infiltration of heart, liver, and kidneys, inasmuch as this parenchymatous change is of frequent occurrence after prolonged anesthesia. But since we have found sim-

ilar severe grades of diffuse fatty infiltration in the liver, myocardium, and kidneys of patients dying with fulminating Graves' symptoms, who had not been subjected to anesthesia and operation, the writer has come to look upon the condition as an essential part of the pathology of severe Graves' attacks, and has explained them in his own mind as the result of acute disturbances in the oxygenation of the body, resulting from or dependent upon the Graves' syndrome. If this be true the fatty degenerative infiltration would be a secondary pathologic lesion of Graves' disease and not a primary one. We have, however, noted from time to time that the livers of Graves' patients show a peculiar form of chronic parenchymatous hepatitis in the form of lymphocyte infiltration, bile duct proliferation, and increase in stroma of the islands of Lissac. These changes may be present in but slight degree, or they may be so marked as to lead to the diagnosis, both upon the gross and the microscopic examination, of an atrophic cirrhosis. From the latter condition, however, this picture differs in that the inflammatory changes are more irregularly distributed in the liver, and also in respect to the more or less well-marked intralobular distribution at the periphery of the lobules, which is present in the more advanced cases. In order to determine the significance of these hepatic changes in

Graves' disease, Weller\* undertook a controlled study of a group of such cases. Forty-four autopsies upon patients showing graves' disease, clinically and pathologically, were selected, taking care to exclude any case which had cholelithiasis, cholecystitis, syphilis or any other associated condition which might produce periportal changes similar to those under investigation. Of this group 6 cases showed no hepatitis, 16 cases showed a slight or moderate hepatitis, while 22 cases showed a well-marked chronic hepatitis of the type described above. A control series of autopsies was then set up, matching each patient with another of the same sex and of approximately the same age, excluding the same group of conditions known to produce pathologic changes in the liver as before, but excluding Graves' disease. In this second series, made to be as nearly equivalent to the first as possible, except that all evidence of a Graves' constitution or syndrome was lacking, 30 cases showed no hepatitis at all, 13 cases a slight or moderate hepatitis, and in only 1 case a well-marked hepatitis. It is significant that this one case was from a patient with a pituitary tumor and well-marked hypoplasia of the adrenals. Such a marked difference in the incidence of hepatitis in the two groups seems to establish the fact that a definite significance attaches to the coincidence of Graves' disease and hepatitis. Whether a direct or indirect relationship exists between them can at present be answered only upon very uncertain hypothetical

grounds. Weller summarizes his findings, as follows: "A well-marked chronic parenchymatous hepatitis was found at autopsy in 22 of 44 selected cases of Graves' disease, while but 1 case of the same degree of hepatic lesion was found in a control series of the same number of autopsies. In the Graves' disease group only 6 showed no evidence of hepatitis, while in the control series 30 out of the total of 44 cases showed no hepatitis. The coincidence of hepatitis with exophthalmic goiter is therefore significant and is in accord with clinical observations of the occurrence of functional disturbance of the liver in cases of Graves' disease." Jaundice has been frequently observed in patients suffering with Graves' disease. Under such titles as "Jaundice Occurring in Persons Suffering from Exophthalmic Goiter," "Acute Yellow Atrophy Associated with Hyperthyroidism," and "Basedow's Disease with Subacute Yellow Atrophy," there have been reported occasional examples of very severe degenerative hepatitis in patients with hyperthyroidism. Less marked degrees of jaundice have likewise been frequently noted, so that it is now well known that many patients with thyrotoxicosis show a yellowish tint of the sclerotics and some a decided icterus. The latter event is thought to have a grave prognostic significance. Studies of impaired liver function in Graves' disease have been carried out by only a few observers. Youmans and Warfield found that 50 per cent of a series of 44 patients with thyrotoxicosis showed an impairment of liver function according to the methods of testing used by them. Loss of weight

\*Presented before the Association of American Physicians, 1930.



was the only feature of the disease which seemed to bear a definite relation to the impairment of liver function. Simonds and Brandes rendered dogs thyrotoxic by heavy thyroid feeding for periods varying from 32 to 100 days. They found that in such animals the liver did not lose weight proportionately with the rest of the body, while with starvation the liver lost weight in greater proportion than the body as a whole. Since the livers of the thyrotoxic animals were practically devoid of glycogen something must occur to counterbalance the loss of glycogen. It was suggested that increased functional activity and increased rate of blood flow might explain the failure of the liver to lose weight proportionately to the body as a whole. There are numerous observations reported in the literature concerning the carbohydrate metabolism in thyrotoxicosis. Cramer was the first to show that the feeding of active thyroid material to rabbits, cats, and rats, led to a lowering or disappearance of the liver glycogen in spite of an abundant carbohydrate food supply. Numerous observers have confirmed this finding. Abeling, Goldener, and Kober showed that the livers of animals fed with thyroxin no longer formed glycogen. If to the diet of these animals during the thyroid feeding, abundant fat was given, the livers again showed glycogen deposits. Ascher and Galvo-Criacho found that in animals made absolutely free of carbohydrate by thyroid-feeding and phloridzin, the addition of fat to the food increased the output of sugar. From this, these authors decided that the hyperthyrotic liver possessed the ability to form

glycogen, but could not fix it, so that after its formation gave it up. The effect of thyroid material upon the carbohydrate state of the organism is so striking that the latter may be made wholly carbohydrate free through the feeding of thyroid material and the use of phloridzin. Not only the liver, but also the muscles are hereby rendered practically glycogen-free. It would appear that not only is the consumption of glycogen increased, but also its new formation and storage. Stimulated by the results of animal experimentation, Kugelman (*Klin Wschr*, August 16, 1930) studied the carbohydrate metabolism of human cases of Basedow's disease. It has been known for a long time that there is an alimentary glycosuria in Graves' disease, this was first described by Kraus and Ludwig. The administration of 100 g of grape-sugar is sufficient to cause a well-marked glycosuria, and the blood-sugar increases and remains at a higher point than is the case in normal individuals. This change in the blood-sugar curve occurs, however, so frequently in so many other diseases that its significance is thereby limited. According to the studies of Bang and Traugott, it would appear probable that this form of "diabetic" blood-sugar curve is found only when the glycogenic function of the liver is damaged. Further investigations of the carbohydrate metabolism of the Basedow cases along the line of the study of the ketone-bodies shows that in thyrotoxic individuals who are given a carbohydrate-free diet for two days, there is such a significant increase of ketone-bodies in the blood as was formerly thought to occur only in sub-

comatose diabetics In the normal individual the fasting value of ketone-bodies never exceeds 3.5 mg per cent of acetone-acetic acid and 5.5 mg per cent of B-oxybutyric acid. In the thyrotoxic patient the fasting value of ketone-bodies rises to 16 mg. per cent of acetone-acetic acid and 18 mg. per cent of B-oxybutyric acid This method of investigation would prove that the Graves' patient has a lowered glycogen-reserve available for metabolism This changed state of the glycogen-depots can be demonstrated also by the study of the blood-sugar curve after intravenous injections of insulin If we inject 10 units of Wellcome's insulin intravenously into a normal man, there occurs regularly in the first ten minutes after the injection an increase in blood-sugar of 15—20 mg. per cent; then a typical fall. Bürger demonstrated that this primary increase of blood-sugar is dependent upon the glycogenic function of the liver In the cases of Graves' disease studied by Bürger's method by Kugelman, none showed this initial hyperglycemia This is further proof of the poverty in glycogen in the hyperthyreotic liver of Graves' disease The study of the blood- and urine-sugar after the oral administration of levulose throws further light upon the processes of the intermediary carbohydrate metabolism Strauss first introduced alimentary levulosuria as a method for testing the liver function Isaac and Adler showed experimentally that of all the organs and cells of warm-blooded animals only the liver is capable of transforming levulose into dextrose According to Isaac the alimentary levulosuria is dependent on the fact that the part of

the levulose which is not converted into glycogen or is burned, in case of functional inability of the liver to convert levulose into dextrose, passes as levulose into the blood and is excreted in the urine. Later investigations of Isaac showed that the occurrence of levulosuria is not sufficient to make a positive diagnosis of disturbed liver function Numerous investigators have shown that the frequently occurring alimentary levulosuria of pregnant women is in most cases a pure renal levulosuria and does not in any way point to a functional disturbance of the liver. Isaac therefore recommended that after the administration of 100 g levulose the blood sugar be determined at varying periods during several hours following its administration. By this method he found that normal individuals showed either no or a very slight rise in blood sugar, but never exceeding values over 120 mg per cent On the other hand in individuals with hepatic disease he found a decided hyperglycemia which persisted for some hours This has been confirmed by Spence and Brett, Bornstein and Holm, Hetényi, Grafe, and others Isaac differentiated the various sugars during this hyperglycemia and found that the height of the blood-sugar after administering of levulose depended in some cases upon an increase in the concentration of dextrose, and in other cases upon an increase in the levulose content of the blood He decided from this that the hyperglycemia, after the administration of levulose, indicates surely a functional disturbance of the liver This has been confirmed by Bodansky who after chloroform and phosphorus poisoning found that the

administration of levulose caused a hyperglycemia. This problem had previously not been attacked from the standpoint of Graves' disease. Falta had reported in a few cases of Graves' disease the occurrence of an alimentary levulosuria. As already shown above this finding is not sufficient evidence of disturbed hepatic function. Abelin and Miyazaki have shown in animal experiments that the administration of levulose in healthy animals produced no essential change in the respiratory quotient, but that the same amount of levulose after thyroid feeding produced a marked increase in the respiratory quotient, even to values of 1.0. They explain this on the ground that levulose, which under normal conditions is only in a small degree oxidized, is, after thyroid feeding, made use of to furnish energy and is fully burned. Kugelman carried out his studies along the lines indicated by Isaac and Grafe. The blood-sugar estimates were made in the morning, the patient fasting, according to the method of Hagedorn-Jensen. After the administration of 100 g levulose, the blood-sugar was taken again at  $\frac{1}{4}$  and  $\frac{1}{2}$  hours. In normal individuals the blood-sugar increased but slightly during the first half hour. Values over 120 mg per cent were never found. At the latest the fasting value had returned after two hours. In patients with Graves' disease, the blood-sugar curve was found to be much higher, reaching regularly values of 160-180 mg per cent. Even after three hours the curve had not fallen to its original value.

The Graves' patients show the same blood-sugar curve as that described by Isaac and Grafe for patients with hepatic disease. From this Kugelman concludes that we can now say with certainty that the thyrotoxic liver suffers not only severe injury in its glycogen depots, but has also lost the capacity to change large amounts of levulose into dextrose and to utilize the latter. For the first time it has been shown that in Graves' disease there is a functional disturbance of the liver which expresses itself in a pathologic condition of the intermediary carbohydrate metabolism. Just what relationship these functional changes bear to the histologic lesions of the liver in Graves' disease remains to be shown. There is a strong possibility that there is a direct relationship between them. The hepatic lesions are probably directly related to the altered metabolic changes associated with thyrotoxicosis. A high basal metabolism has become an almost over-rated symptom of Graves'. The investigation of the gaseous interchange and the information it gives us as to metabolism is only a small part of the whole metabolic process, but throws no light upon the essential changes in the intermediary metabolism. These evidences, both pathologic and functional, of the disturbed glycogenic function of the liver, are, therefore, of prime importance, and further studies along these lines may throw important light upon what lies behind the thyroid in the pathogenesis of the Graves' syndrome.

## Abstracts

*Changes in the Blood Chemistry in Malignant Disease with Special Reference to Carbohydrate Tolerance and Alkalosis* By PAULINE BEREGOFF (The Jour of Cancer Research, October, 190).

The purpose of this investigation was to observe the alterations in the blood chemistry associated with malignant disease, and to determine the value of such changes in the diagnosis of human cancer. Freund (1885) and Trinkler (1890) found in cancer patients a low tolerance for sugar and claimed that the carbohydrate tolerance test was of diagnostic value in cancer. Rohdenburg, Bernard, and Krehbiel (1919) studied the sugar tolerance in cancer patients and found a low tolerance for sugar in all cancer patients examined, but as their series was small, they did not base any contentions on their findings. In the same year Edwards reported several cases of carcinoma in which the glucose tolerance test was low. He considered this test of greater value as a method of eliminating the presence of cancer than of establishing its existence. The failure to establish a specific glucose tolerance curve, as is found in cancer, he considered strong evidence against the presence of malignant disease. In 1927, Reding and Slosse showed that cancer patients possess a lower tolerance to glucose. In 1928, Reding attempted to demonstrate alterations in the blood chemistry of patients suffering from cancer or having a predisposition to cancer. In each case he determined the pH, the total  $\text{CO}_2$  (free and combined) and the concentration of the ionized calcium. Alkalinity, fall of  $\text{CO}_2$ , and fall in the concentration of ionized calcium, he found to be constant phenomena associated with cancer. In 1929 these findings were confirmed by Reding and Slosse. In the same year Schreus also reported that the blood chemistry of carcinoma patients showed a moderate alkalosis. Cori and Cori have pointed out that abnormally large

amounts of glycogen are present in malignant tumors. Warburg showed that there is a distinct difference in glycolysis of the cancer cell as compared with glycolysis in normal tissues. The glycogen metabolism of cancer is about 8 times that of working muscle and about 100 times that of resting muscle. According to Warburg and Cori and Cori the excessive amount of lactic acid produced by cancer cells points to abnormal carbohydrate metabolism in the cancer cell itself, whereas the observations indicate an abnormal carbohydrate metabolism in the organism as a whole. Jackson claims that the character of the sugar curve may serve as an indicator of the response that may be expected to radiation and surgery. Beregoff studied a series of 300 patients in whom the blood showed a tendency towards alkalosis, low carbohydrate tolerance, deficiency in calcium, and a low carbon dioxide content. All bloods of cancer patients examined in this investigation exhibited a positive carbohydrate curve and a tendency towards alkalosis. However, positive carbohydrate curves were obtained in other pathologic states, such as hyperthyroidism, acromegaly, and diabetes, but in these conditions no alkalosis was demonstrable. As an indication of the presence of malignant disease a positive carbohydrate curve is significant only in the presence of alkalosis. Examinations of the blood of 25 individuals not suffering from cancer, and without family history of cancer, yielded a negative carbohydrate curve in every instance and the pH of the bloods was within normal limits. The concentration of the ionized calcium averaged 226 mgm. per liter. It would appear from these experiments that the carbohydrate tolerance test and the hydrogen ion concentration are of greater value in eliminating the presence of malignant disease than of proving its existence.

*The Clinical Value of Tests of Liver Function* By GEORGE MORRIS PIERSOL (Canad Med Assoc Jour, October, 1930, p 524).

Piersol sums up his discussion of hepatic functional tests as follows. From his experience with liver function tests, as applied to a considerable group of patients suffering from various disorders, the three most practical and useful tests clinically are (1) the retention of the dye bromsulphthalein, (2) the estimation of the serum bilirubin, particularly, the determination of the icterus index, and (3) the occurrence of urobilinogen in the urine. The retention of bromsulphthalein is not an early indication of liver dysfunction. The degree of retention is a helpful indication of the extent of liver damage. When dye retention occurs other functional tests are also positive, but we have not found any noteworthy degree of bromsulphthalein retention when the ordinary clinical evidences of liver disease were not present. The estimation of the serum bilirubin is a most useful test of liver function, since it frequently indicates the presence of a latent icterus before liver disorders can be recognized by clinical signs, and the persistence of bilirubin in the blood after all other evidences of liver disease have disappeared. He regards an increase in the urobilinogen as the most delicate test of impaired function. Urobilinogen is increased even when damage to the liver parenchyma is exceedingly slight. It is persistently increased as long as any residual hepatitis remains, and it is the one test which has been positive in a certain number of cases in which liver disease was suspected, but could not be proved clinically. Because of the liver's multiple functions and because of its extraordinary capacity and remarkable ability to regenerate, it must be admitted that from the standpoint of the clinician who is seeking some means whereby impaired liver function can be recognized, before gross clinical evidences of liver disturbance occur, the tests for liver function that are available at present have hardly justified our earlier expectations. This is the more true because in all focal lesions of the liver, especially those without biliary obstruction, functional tests yield no useful information. They are, however, of some help in differentiating the various types of jaundice and in the diffuse

disturbances of the liver, in which by means of them, we are enabled to estimate with some degree of accuracy, the extent and duration of the liver damage, so that they are undoubtedly of prognostic value.

*Uroselectan as a New Renal Functional Test* By W. TOURNÉ and E. DAMM (Klin Wschr, August 23, 1930)

The uroselectan blood-curve falls steeply in the first two hours, less steeply later. When the renal function is normal no more uroselectan is present in the blood after 4 hours. Values under 0.5 g after 4 hours indicate a low grade of renal insufficiency. Values over 0.5 g indicate a higher grade of renal damage. According to the degree of renal insufficiency more or less large amounts of uroselectan are found in the blood. The use of the 4 hour uroselectan test in the blood is recommended as a new test for urinary retention.

*The Treatment of Cardiac and Aortic Syphilis* By A. MEYER (Münch Med Wschr, 1930)

The treatment of syphilitic myocarditis and aortitis by means of salvarsan is, according to Meyer, not always devoid of harm, and may lead to unpleasant consequences through the development of the Herxheimer reaction. He advises that patients having aortic and cardiac syphilis be given a milder form of antisyphilitic treatment in the form of a "Schmierkur", or intramuscular injections of bismuth, or by internal medication with iodide. When salvarsan is used it should not exceed 5-6 g for the total amount employed. The treatment should be intermittent and extended over prolonged periods. R. Fischer (Wien Klin Wschr, 1930) believes that the suspicion of aortic syphilis, even in the presence of a negative Wassermann, is sufficient to justify active treatment. An electrocardiogram is necessary to show the condition of the coronary arteries. If this shows coronary disease, antisyphilitic treatment is absolutely contra-indicated. Neosalvarsan is the best remedy for the treatment of aortic syphilis. Fischer gives it at weekly intervals in doses of 0.075, 0.1, 0.15, and 0.3 gm. When aortic insufficiency is present, with slight changes in the electrocardiogram of

the left ventricle, after the dose has reached 0.3 g., this should be repeated only monthly, in order to give the heart time to compensate, by the development of the collateral circulation, for the cicatricial narrowing of the coronary arteries.

*Investigations as to the Place of the Liver in the Intermediary Metabolism* By KARL PASCHKIS (Klin. Wschr., October 11, 1930).

The rôle played by the liver in protein metabolism remains still an unsolved problem. The protein material of the food is either wholly or for the greater part broken down in the intestine to the simple fundamentals, the amino-acids, and carried in this form through the portal vein to the liver. It is a question whether desaminization of the amino-acids is one of the functions of the liver, or whether this process occurs in the peripheral tissues. Van Slyke, Folin, and Denis hold different views on this matter. Mann and Magath have proved experimentally that the dog deprived of his liver cannot desaminize the amino-acids. Clinically, the important question is whether in individuals with hepatic disease any disturbance of protein metabolism takes place. In acute yellow atrophy, as well as in many cases of simple jaundice, leucin and tyrosin appear in the urine, but this may be the result of the associated organ autolysis and not the result of a lowered power of desaminization on the part of the liver. Glässner some years ago found that the administration of amino-acids to patients with liver disease led to an increased output in the urine. Other investigators have had for the greater part negative results. All of these experiments which are based upon the intravenous administration of amino-acids are worthless, because of their wholly unphysiologic character. Paschkis has systematically administered amino-acids perorally to patients with liver disease, particularly to those showing a simple icterus following the administration of neosalvarsan for treatment of secondary lues. Most of these experiments were made with glykokoll, others with leucin, alanin, and asparaginic acid. The amino-acid content of the blood was taken before the experiment, and at intervals of 1, 2, 3, 4, and 5 hours after-

wards, by the colorimetric method of Folin. Normal controls show after the oral administration of 50 g. glykokoll an increase of the amino-N in venous blood. This increase is much higher in most cases of simple icterus. When the procedure was repeated after the disappearance of the icterus the increase is much less. For example, one patient with simple icterus at the height of the affection, showed after the administration of 50 g. glykokoll an increase of the blood amino-N of over 22 per cent over the fasting content. After the disappearance of the jaundice the same experiment produced a rise of only 33 per cent. No marked parallelism with disturbance of other functions of the liver was shown either with carbohydrate assimilation or with the elimination of bile-pigment. The pathologic amino-acid curve persisted after the icterus. In liver cirrhosis, the height of the rise can be affected by the lessened absorption due to the portal stasis. The amino-N value of the peripheral venous blood is dependent naturally not only on the liver function, but in these investigations the renal component and the renal threshold for amino-acids may be ignored, since in the cases studied there were no complications on the part of the kidneys. On the other hand the absorption capacity of the peripheral tissues plays a rôle. Since, however, the extreme curves were found only in patients with liver disease, and after the disappearance of the liver affection the alimentary amino-acidemia was again slight, the curves obtained may be taken as demonstrating a functional disturbance of the liver.

*Clinical and Therapeutic Experiences in 650 Cases of Pneumonia* By C. E. SCHUNTERMANN (Med. Klin., 1930)

Croupous pneumonia due to pneumococci is a disease of middle life, 20-40 years. The relation of males to females affected is about 4:2. The mortality for the individual ages varied from 8.6 to 15.3 per cent in a curve from 18 to 40 years. More cases occurred in the first four months of the year than in the later ones. The lower lobes were most frequently involved, the right more often than the left. The prognosis was determined by biologic factors. Double-sided pneumonias or cases with involvement of the upper lobes

showed a greater mortality. The most important factor in the treatment was complete psychical and bodily rest. Further, the treatment consisted in combating the toxic component and in assisting the heart and vasomotor system. The use of quinine lowered the mortality. Quinine-urethane and solvochin were employed. The use of quinine should be begun as early as possible. By doing so postpneumonic complications may be avoided.

*Syphilis of the Stomach as Seen Roentgenologically* By J. G. SCHLIFFER (Arch Verdauungs Krankh, 1930)

The anatomical changes produced by syphilitic affections of the stomach may be visualized by x-ray examination. The differential diagnosis is difficult, however, because of the similarity of the syphilitic affections to those of other organic diseases of the stomach. Gummatous infiltration and hyperplasia and the syphiloma have their seat in the submucosa in the great majority of cases. In gummatous hyperplasia one sees a circular narrowing of the affected part. The contours are sharply delineated. The central canal

lies centrally and runs straight. Peristalsis is diminished or absent. The barium meal passes the narrowed portion without hindrance and quickly. Under specific treatment these changes lessen or wholly disappear. Contraction processes when predominating tend to progress. Roentgenologically, the stenosed portion becomes narrower, the contours sacculated, the central canal is displaced somewhat, and the passage of material often markedly hindered. In the reversible form three types may be distinguished: 1, the prepyloric type (caneen stomach), 2, the median type (hour glass stomach), and 3, the total type (microgastria). In the irreversible form there are also three types: 1, pylorus stenosis, 2, cicatricial hour-glass stomach, 3, syphilitic total contraction of the stomach (microgastria). Gummas and gummatous ulcers are distinguished roentgenologically by the atypical character of the picture. Of significance is the determination of the presence of marked anatomical changes wholly out of proportion to or even contradictory to the clinical picture.

## Reviews

*Physiological Chemistry* A Textbook and Manual for Students By ALBERT P. MATHEWS, Ph.D., Carnegie Professor of Biochemistry, University of Cincinnati. Fifth Edition. 1223 pages, 107 figures. William Wood and Company, New York, 1930. Price in cloth, \$7.00.

This new edition has much new matter added, particularly in the chapters on the vitamins, the internal secretions, the carbohydrates, the porphyrins, the bile pigments and the bile salts. The progress that has been made in our knowledge of the enzymes has also been added. The important isoprene, or polydrene, syntheses are brought in for the first time. The only revision of nomenclature has been the change of the term lipin to lipid. Part I treats of the chemistry of protoplasm and the living cell under the following heads: Chapter I, The General Properties of Living Matter; Chapter II, The Glucides or Carbohydrates; Chapter III, The Lipids: Fats, Oils, Waxes, Phosphatides, Sterols; Chapter IV, the Proteins; V, the Physical Chemistry of Protoplasm. Part II treats of the mammalian body considered as a machine, its growth, maintenance, energy transformations, and waste substances, under the following heads: Chapter VI, Animal Heat; Chapter VII, The Raw Materials or Foods; Chapter VIII, Salivary Digestion; Chapter IX, Digestion in the Stomach; Chapter X, Digestion in the Intestine; Chapter XI, Absorption; Chapter XII, The Circulating Tissue: The Blood; Chapter XIII, The Master Tissue of the Body: The Brain; Chapter XIV, The Contractile Tissues: Muscle; Chapter XV, The Connective or Supporting Tissues: The Bones, Cartilage, Teeth, Connective Tissue; Chapter XVI, The Cryptorrhetic Tissues: The Thyroid, Parathyroid, Hypophysis, Suprarenal, Reproductive Glands; Pineal Gland, Thymus,

Chapter XVII, The Skin and Eye; Chapter XVIII, The Excretions of the Body: Urine; Chapter XIX, The Metabolism of the Body Considered as a Whole: Carbohydrate Metabolism; Chapter XX, Protein Metabolism of Body; Chapter XXI, Metabolism Under Various Conditions: Vitamins; Chapter XXII, Respiration; and Chapter XXIII, Chemical Defense Against Disease. Part III is concerned with practical work and laboratory methods. Each chapter is followed by a list of papers bearing on the subject treated in that chapter. The material of the book appears to be full and brought up-to-date. The author has expressed himself in a clear and concise style. The book is readable and understandable. Five editions since 1915, and an Italian and Spanish translation speak for a successful reception. The 337 experiments outlined under practical work cover thoroughly the field of laboratory work in biochemistry. The directions given for each experiment are sufficient and to the point. Superfluous and extraneous matter is omitted. This book can be recommended without reserve to the student in physiological chemistry, and to the physician who wishes to refresh and to add to his knowledge of the subject.

*Handbook of Pediatric Procedures* By FRANCIS SCOTT SMYTH, M.A., M.D., Associate Professor of Pediatrics, University of California, Pediatrician-in-Chief, University of California Hospital and Out-Patient Department, and Edith I. M. Irvine-Jones, M.B., Ch.B., Instructor in Pediatrics, Washington University School of Medicine, Assistant Physician, St. Louis Children's Hospital. 212 pages. The MacMillan Company, New York, 1930. Price in cloth, \$2.50.

The publication of this book has been prompted by the apparent demand for brief



descriptions of methods for the study and treatment of disease in children. The outline form and didactic presentation of the material have been adopted for the sake of brevity and ease in reference. The treatment of the material falls into Section A—Diagnosis, three chapters being devoted to History, Physical Examination, and Laboratory Diagnosis, Section B—Therapy, containing seven chapters treating successively of Dietetic Therapy, Biologic Therapy and Prophylaxis, Physical Therapy, Drug Therapy, Fluid Introduction in Sick Children, Emergency Treatments and Some Common Principles. This book is in reality a small and much condensed manual of pediatrics, and has all of the defects of such abbreviations. Such may have a certain value as a convenient pocket aid to memory for internes in pediatrics, but if, as the preface would indicate, there is a demand for brief outlines of this type among practitioners, one is led to believe that a superficial machine type of knowledge is a desideratum.

*Intestinal Tuberculosis* Its importance, Diagnosis, and Treatment. A study of the Secondary Ulcerative Type. By LAWRA-SON BROWN, M.D., Consultant to the Trudeau Sanatorium, Saranac Lake, New York, and Homer L. Sampson, Roentgenographer of the Trudeau Sanatorium, Saranac Lake, New York. Second edition, Thoroughly Revised. 376 pages, 122 engravings, and 2 colored plates. Lea and Febiger, Philadelphia, 1930. Price in cloth, \$4.75 net.

This second edition has been fully revised and enlarged. The methods of examination are described in greater detail than in the first edition. The essentials of the diagnosis are summarized in a few pages, illustrated by diagrams and references to the plates. This greater attention to methods of examination is considered necessary by the authors, who feel that because the diagnosis depends essentially upon roentgenologic methods, the ordinary physician is not sufficiently experienced in such methods and needs detailed descriptions of methods. The recent anatomical and physiological knowledge of the intestinal tract is also given in

greater detail. This second edition amplifies and revises in the light of later knowledge and experience the clinical studies upon which the first one was used. The basic principles stand however. The widespread appreciation of the book is responsible for this new edition. The publication of the first did much to stimulate interest in the study of intestinal tuberculosis, and the methods of diagnosis and treatment which it described have been chiefly responsible for the lifting of intestinal tuberculosis out of the realm of hopeless diseases into that of remedial affections. It was, therefore, primarily responsible for this marked change of attitude toward intestinal tuberculosis, which was almost universally formerly regarded as one of the hopeless sequelae of pulmonary tuberculosis. The frequency with which pulmonary tuberculosis is complicated by intestinal tuberculosis is well known to pathologists. It occurred to the authors that this complication might not always be a terminal condition, but might occur early enough in the course of the pulmonary infection to diminish greatly the chances of recovery from the lung lesion. The difficulty of diagnosis of the intestinal infection explains why for so many years the intestinal involvement has received so little attention from students of tuberculosis. The methods of diagnosis described in this book have led to a radical change in the point of view. Out of 5,542 patients examined roentgenologically for intestinal tuberculosis, 1,465 were found to be suffering from it. The material of the book is arranged as follows: Chapter I, The History of Intestinal Tuberculosis; II, The Anatomy of the Intestines; III, The Normal Physiology of Intestinal Movement, IV, V, VI, and VII, Pathological Anatomy of Intestinal Tuberculosis; VIII, Pathological Physiology of Movement, IX, Etiology of Intestinal Tuberculosis, X, Experimental Intestinal Tuberculosis; XI, Importance and Frequency of Secondary Intestinal Tuberculosis; XII, Site of the Lesions in Intestinal Tuberculosis; XIII, Primary and Secondary Intestinal Tuberculosis; XIV and XV, Clinical Symptoms of Intestinal Tuberculosis; XVI, Clinical Examination of Intestinal Tuberculosis;

XVII, Relation of the Symptoms of Intestinal Tuberculosis to the Site of the Lesion, XVIII, The Abdominal Examination in Intestinal Tuberculosis; XIX, The Pulmonary Condition in Secondary Intestinal Tuberculosis, XX, XXI, XXII, and XXIII, Diagnosis of Intestinal Tuberculosis, XXIV, Complications of Intestinal Tuberculosis, XXV, Prognosis, XXVI, Prophylaxis, XXVII, Treatment, XXVIII, Conclusions and Summary. Roentgen-ray methods of diagnosis of first importance in intestinal tuberculosis are discussed in Chapters XXII and XXIII. Of all the complications of pulmonary tuberculosis, intestinal infection is the most frequent. A knowledge of intestinal tuberculosis is therefore essential for any physician who attempts to treat pulmonary tuberculosis. Until the roentgen-ray diagnosis was perfected, no one was able to state when in the course of a pulmonary tuberculosis, intestinal tuberculosis began, for it may be present for a long time without giving rise to symptoms. If it were only a terminal infection arising when all hope of recovery has vanished, its importance would be much less than it is today, since we know that intestinal infection may complicate very early cases, and is much more common among the moderately advanced, and very frequent in the advanced and terminal stages of pulmonary tuberculosis. It is for these reasons that this book is so important for the practitioner who treats cases of tuberculosis. Hypermotility with filling-defects indicates an ulcerative condition of the bowel, which in the presence of pulmonary tuberculosis is practically always of a tuberculous nature. The absence of hypermotility and filling-defects excludes for practical purposes the presence of tuberculous colitis. Digestive disturbances in the patient with pulmonary tuberculosis are always suspicious. It is now possible, by using the author's methods to decide whether these are functional or due to organic disease in the gastro-intestinal tract. To every physician who treats cases of pulmonary tuberculosis, this book is a necessary part of his armamentarium.

*Edward Jenner and the Discovery of Smallpox Vaccination*. By LOUIS H. ROBBIS.

Lieutenant Commander, Medical Corps, United States Navy. Reprinted from *The Military Surgeon*, Vols. 65 and 66 155 pages, 11 illustrations. George Banta Publishing Company, Menasha, Wisconsin, 1930. Price in cloth, \$1.00.

This little volume is a well-written and interesting history of smallpox inoculation and vaccination, and particularly of Edward Jenner and the great part he played in the establishment of the knowledge of protection against smallpox. The historical knowledge of this disease up to the time of Jenner is first briefly sketched, and this is followed by a detailed history of inoculation as a preventive method, giving of course, due mention to Lady Mary Wortley Montague and the part played by her in the introduction of this method of prevention into England. Boylston, the first advocate of inoculation in North America, and Benjamin Franklin's "Some Account of the Success of Inoculation for the Smallpox in England and America," published in 1754, are given full credit for their share in spreading the use of this method on this side of the Atlantic. Chapter IV then takes up the life of Edward Jenner, his birth and education, and association and friendship with the Hunters. In 1771 Jenner returned to Gloucestershire to begin practice as a country doctor. He was essentially a country bred man, fond of country people and country life. Upon this choice of country practice as against practice in London, the most significant achievement of Jenner's scientific life depended. The observations which led to the discovery of smallpox vaccination could only have been made in a rural locality where dairymaking was carried on. Had Jenner remained in London at Hunter's suggestion, this chance would in all probability have been lost, and vaccination have remained undiscovered. An interesting picture is given of Jenner's life in Gloucestershire, his interest in natural history and music, his excursions into the realm of poetry, his domestic and professional life, etc., are all sketched in an entertaining and lively manner. Then comes the story of cowpox and Benjamin Jesty, the Dorset farmer, who first vaccinated with cowpox material. His wife was the first person in England known to have been in-

tentionally vaccinated with cowpox Jenner's claims to distinction rest upon the fact that he took the countryside tradition of farmers and dairymaids, which other medical men ignored or scoffed at, studied the matter for nearly twenty-five years, experimented, observed, and recorded his findings, overcame all antagonism and opposition, and eventually succeeded in making of the countryside tradition a practical and usable medical procedure Upon this fact his fame is firmly fixed for all time The remainder of the book is taken up with the story of the spread of vaccination throughout the world, and of the last years and death of Jenner This little volume gives a remarkably full account of Jenner's life and work, told in an interesting and lively manner, it holds the reader's attention from beginning to end It is a chronicle of one of the greatest achievements of medicine, the work of a country practitioner, a never-to-be-forgotten fact We recommend this little book to all of those who have an interest in the history of the development of medicine

*History of Haitian Medicine* By ROBERT P PARSONS, Lieutenant-Commander, MC, USN With a Foreword by EDWARD R STARR, Rear Admiral, MC, USN 196 pages, 21 illustration, and a folding map of Haiti Reprinted with additions and corrections from *Annals of Medical History*, 1929 Paul B Hoeber, Inc, New York, 1930 Price in cloth, \$2.25 net

This history was written in its original form in January, 1929, and appeared in that form in the May number, 1929, of the *Annals of Medical History* Its publication aroused much interest, and this, with the recent prominent position of Haiti in the public eye, led to its publication in this form Haitian history is a tale of turbulence, warfare and bloodshed, of intrigue and political factions, of comic opera revolutions, and of thinly-veneered civilization Scratch its surface and one finds beneath it the savagery of Central Africa and the superstitious horrors of voodooism The tom-tom still reverberates in the outlying mountainous recesses, and the Haitian blacks still celebrate the indecent orgiastic rites of their degenerate and primitive religion Per-

haps nowhere else in the world do the extremes of savagery and civilization meet as they do upon this island Corresponding to the ignorance and illiteracy of the native population is their physical condition Parsons describes the island as having been a veritable hotbed of diseases from the ravages of which some three million people in Haiti suffered Almost every one of the rural population has had malaria, yaws, and intestinal parasites Yaws, in particular, has been the physical curse of Haiti—first cousin to European syphilis, if not the same disease modified by age incidence, environment, and racial differences For these diseases, until recently, there was no medical relief available Up to ten years ago the mass of the Haitian people, to the number of three millions, was universally diseased, ill, crippled and weakened, helpless and hopelessly resigned to their lot Parsons traces the thread of medical history, it falls logically into three principal periods the French colonial period during the 17th and 18th centuries, the independent period from 1804-1915, and the period of American occupation since 1915 During the French colonial period there was little progress in Haitian medicine The French physicians practiced among the classes of citizens who could afford to pay, or superintended in a very superficial way the medical treatment of the slaves During the independent period the development of medicine was pathetically slow and interrupted by the numerous revolutions and successions of rulers Particularly pathetic were the attempts to develop medical schools and hospitals Among the influences for good was the American physician Lowell, who practiced medicine in the island from 1833-1845 Not until about 1890 was real progress made in the development of the medical school, and there began to be a scientific spirit in the practice of medicine and a scientific outlook on medical study In this renaissance the leading spirit was Dr Leon Audam In the period from 1900 to 1910 original papers from Haiti appeared in French medical literature, a medical journal, "*La Lanterne Médicale*" was published for two years, and records of health conditions were made From 1910-1915 there were seven different presidents in office, each suc-

ceeding one found the country sinking further down toward anarchy. Naturally the medical profession, medical school, and hospitals shared in this down-hill course; and when the Americans came in 1915, conditions were desperate and most deplorable. The sanitary problems confronting us were the greatest of all. Particularly was the yaws situation the great medical problem of the land. This was, however, not clearly

realized until the arrival of Dr. Paul W. Wilson in 1922. The story of what the American occupation has done medically for Haiti is a wonderful one, and the book is worth reading for this story alone. Nevertheless, the final chapter on Haitian doctors leaves one pessimistic and apprehensive as to the final outcome of the contact of two cultures so diverse and so intrinsically opposite as the American and the Haitian.

## College News Notes

Dr Leo V. Schneider (Fellow) has resigned as Resident Physician at the State Sanatorium of Maryland, and accepted an appointment as Health Examiner for the Playground Athletic League of Baltimore, Maryland. His present residence is 3716 Springdale Avenue, Baltimore.

In the September Issue of the American Review of Tuberculosis Dr Schneider contributed an article on "Primary Aspergillosis of the Lungs"

At the twenty-fourth annual meeting of the Seventh District Branch of the Medical Society of the State of New York, held at Keuka College, Penn Yan, N Y, September 25, the following Fellows participated

Dr George L. Eckel, Buffalo (by invitation), "Anterior Poliomyelitis"

Dr Wardner D. Ayer, Syracuse, discussion of the above paper,

Dr James E. Talley, Philadelphia (by invitation), "Care of the Heart in Certain Infections",

Dr John J. Finigan, Rochester, discussion of the above paper

Dr C. Harvey Jewett (Fellow), Clifton Springs, is the First Vice President, and Dr John A. Lichty (Fellow), Clifton Springs, is the Secretary of the above society

Dr John A. Lanford (Fellow), Assistant Professor of Bacteriology and Pathology at the Tulane University of Louisiana School of Medicine, was guest of honor on the clinical program of the Northwest District (Alabama) Medical Society, October 3-4

Dr Robert S. Berghoff (Fellow), Chicago, addressed the McLean County (Ill.) Medical Society, September 9, on "Syphilis of the Heart."

Dr Elliott P. Joslin (Fellow), Boston, delivered a paper on "Symptomatology and

Treatment of Diabetes," October 7, at the meeting of the First District Branch (N. Y.) Medical Society's meeting in New York City

Dr James B. McElroy (Fellow), Memphis, spoke on "Ascites" at the Tri-County Medical Society of Tennessee, September 18

Lieut. Col. William S. Shields (Fellow), M. C., U. S. Army, has been transferred from Fort Sam Houston, Texas, to the Fitzsimons General Hospital, Denver

Dr Laurence R. DeBuys (Fellow), New Orleans, is President-Elect of the American Pediatric Society

Dr Edwin C. Ernst (Fellow), St. Louis, President of the Radiological Research Institute, recently announced the incorporation of the Institute. Among their projectives is the production of x-ray tubes of a power now unavailable, in order that deeper penetration and faster action may be obtained. "Other objects of the society are cheaper radium, American control of its own radium supply, establishment of a central radiological research laboratory, fostering pure radiological research in colleges, co-operating with the National Institute of Health created by Congress, and establishment of an advisory board of fifty scientists to extend the practical application of x-ray research to all walks of life"

Dr William S. Thayer (Fellow), Baltimore, was one of the invited guests to address the 61st annual session of the Medical Society of Virginia at Norfolk, October 21-23

Other Fellows of the College who appeared on the program were

Dr Robert Finley Gayle, Richmond—"The Management of the Psychoneurotic",

Dr. David C. Wilson, University—"The Care and Prognosis of Extra-Mural Epileptics."

Dr. James W. Hunter, Jr (Fellow), Norfolk, was host to members of the Virginia Roentgen Ray Society at a luncheon during the annual session of the Medical Society of Virginia.

Dr Walter E Vest (Fellow), Huntington, W Va, President of the Alumni Association of the Medical College of Virginia, acted as Chairman of the Annual Alumni Luncheon, also during the meeting of the Medical Society of Virginia

At the opening Convocation of the Medical College of Virginia, on September 17, Dr. Vest made an address on "Student Obligations"

Dr. W. A. Bloedorn (Fellow), Washington, D C, addressed the Loudoun County (Va) Medical Society, September 9, on "New Cardiac Aspects and New Cardiac Therapeutics"

Dr. F. C Rinker (Fellow), Norfolk, Va, is Secretary of the Second District (Va) Medical Society

Dr C L Harrell (Fellow), Norfolk, Va, presented a paper before the quarterly meeting of the Southside Virginia Medical Association, September 9

Dr Noble Wiley Jones (Fellow), Portland, Oregon, with Dr Dorwin L Palmer, is the author of an article entitled "Observations Upon Chronic Cholecystitis With Special Reference to Motor Disturbances of the Gastro-Intestinal Tract in Relation to Preoperative and Postoperative Symptoms," appearing in the October Issue of the American Journal of The Medical Sciences

Dr I Seth Hirsch (Fellow), New York, N Y, Dr Laurence H Mayers (Fellow), Chicago, Ill, and Dr Albert Soiland (Fellow), Los Angeles, Calif, are authors of the following papers or reports in the October Issue of Radiology, respectively "Urography By Uroselectan," "A Concept of Arthritis"

and "The Annual Meeting" (Radiological Society of North America).

Dr. Harold I Reynolds (Fellow), Athens, Ga., and Dr Trimble Johnson (Fellow), Atlanta, Ga, are authors of "Acute Poliomyelitis" and "Belladonna in Abdominal Diagnosis and Treatment," appearing in the September Issue of the Journal of the Medical Association of Georgia

Dr Stewart R Roberts (Fellow), Atlanta, Ga, addressed the Ninth District Medical Society of Georgia at their September meeting on "Hypertension"

Dr. Harold I Reynolds (Fellow), Athens, Ga, is President of the Eighth District Medical Society of Georgia

Dr Frank Garm Norbury (Fellow), Jacksonville, Ill, addressed the Morgan County (Illinois) Medical Society, September 11, on "Medical Observations Abroad"

Dr Felix J Underwood (Fellow), State Health Commissioner of Mississippi, addressed the Indiana State Board of Health at Fort Wayne, September 22-24, on "Results Accomplished by Full-Time County Health Departments"

Dr Colonel B Burr (Fellow), Flint, Mich, was the recipient of a complimentary dinner at Benton Harbor, Mich, by the Officers and Council of the Michigan State Medical Society on September 16

At the meeting of the Second Councilor District Medical Society of Ohio, held at Dayton, September 24-26, the following Fellows of the College delivered the addresses indicated

Dr Stewart R Roberts, Atlanta, Ga—"Essential Hypertension, Well Established," "Hyperthyroidism with Accent on the Thyroid Heart Previous to Operation" "The Nervous Heart Without Organic Heart Disease Particularly if Vague Pains in the Left Precordium Are Present" "Agranulocytosis Clinical Onset, Symptoms, Treatment," "Failing Heart and Its Realization" and "The

Heart and Circulatory Complications of Pregnancy"

Dr Walter C Alvarez, Rochester Minn —"Diagnosis of Gastro-Intestinal Disease" and "Treatment of Organic and Functional (Digestive) Disease"

Dr Ralph Pemberton (Fellow), Philadelphia, Pa, addressed the Northwestern Ohio Medical Society at Toledo, October 27, on "Arthritis"

Dr Chester W Waggoner (Fellow), Toledo, Ohio, President of the Ohio State Medical Association, addressed the same organization on "The Importance of the Practice of Medicine to a Community"

Dr Frank Norman Wilson (Fellow), Ann Arbor, Mich, delivered an address entitled "Cardiac Weakness and Cardiac Failure" at the Annual Mercy Day at the Mercy Hospital, Pittsburgh, Pa, September 24

Dr Henry M Ray (Fellow), Pittsburgh, Pa, spoke on "Clinical Significance of Spinal Fluid Examination, with Special Reference to Neurosyphilis" before the South Hills Branch of the Allegheny County Medical Society, September 18

Dr James C Naurison (Fellow), Springfield, Mass, addressed the Windham County Medical Society (Vermont), recently, on "Diseases of the Heart"

Dr Winthrop Adams (Fellow), who has been Medical Director of the United States Veterans' Bureau, has been assigned, at his own request, as Medical Officer in Charge of the Veterans' Neuropsychiatric Hospital at Bedford, Mass

Dr Henry I Kloop (Fellow), Allentown, Pa, Superintendent of the Allentown State Hospital, delivered the Annual Report before the Homeopathic Medical Society of the State of Pennsylvania at Harrisburg on September 25

Gifts of the following reprints to the College Library of publications by members are duly acknowledged as follows

Dr Donald L Hamilton (Fellow), Sayre, Pa,

Reprint—"Aneurysm of Anterior Cerebral Artery"

Dr I S Kahn (Fellow), San Antonio, Texas

3 Reprints—"Bronchial Asthma"

"The Intravenous Use of Epinephrin in Severe Bronchial Asthma"

"Tree Pollen Hay Fever and Asthma in the South"

Dr Edgar F Kiser (Associate), Indianapolis, Ind

2 Reprints—"Bronchomycosis"

"Pleural Effusion Associated with Congestive Heart Failure Localized in an Interlobar Space"

Dr Carl V Fischer (Fellow), Philadelphia, Pa

Reprint—"A Survey of the Progress in Internal Medicine, 1929"

Dr G Morris Golden (Fellow), Philadelphia, was the Chairman of the Section on Clinical Medicine and Pediatrics at the Sixty-seventh Session of the Homeopathic Medical Society of the State of Pennsylvania, held at Harrisburg, September 25-27

Dr Francis M Pottenger (Fellow), Monrovia, Calif, attended the meeting of the Canadian Tuberculosis Association at Nipette, Manitoba, August 23, where he delivered an address on the subject of "The Relationship of the Vegetative Nervous System to Symptoms of Pulmonary Tuberculosis" About fifty tuberculosis workers were guests at this meeting

Dr Carl V Vischer (Fellow), Philadelphia, read a paper, "Modern Advances in General Therapeutics," before the Homeopathic Medical Society of the State of Pennsylvania at its Sixty-seventh Session at Harrisburg, September 25

Dr E W Anderson (Associate), formerly of the Mayo Clinic, has recently become associated with the Hitchcock Clinic of Han-

over, N. H., and is an instructor in medicine in the Dartmouth Medical School.

At the Minneapolis meeting of the Interstate Postgraduate Medical Association of North America, held October 20-24, 1930, the following Fellows of the American College of Physicians took part as indicated below.

Dr. Henry A. Christian, Boston, Mass.—

A Medical Diagnostic Clinic and an address, "Clinical Types of Nephritis";

Dr. Harlow Brooks, New York, N. Y.—

A Medical Diagnostic Clinic and an address, "The Periodical Physical Examination";

Dr. Elliott P. Joslin, Boston, Mass.—A

Medical Diagnosis Clinic and an address, "Unclassified Glycosurias—Their Significance and Outcome";

Dr. Fritz B. Talbot, Boston, Mass.—A

Pediatric Diagnostic Clinic and an address, "The Dietary Treatment of Epilepsy in Children";

Dr. William A. White, Washington, D. C.—

An address, "Psychoses of Different Age Periods";

Dr. Emanuel Libman, New York, N. Y.—

A Medical Diagnostic Clinic and an address, "Coronary Thrombosis and its Sequelae";

Dr. Charles A. Elliott, Chicago, Ill.—A

Medical Diagnostic Clinic and an address, "Late Results of Thyroidectomy for Hyperthyroidism";

Dr. George E. Brown, Rochester, Minn.—

A Diagnostic Clinic,

Dr. John H. Musser, New Orleans, La.—

A Medical Diagnostic Clinic and an address, "Anemias Simulating Pernicious Anemia";

Dr. Elsworth S. Smith, St. Louis, Mo.—

An address, "The Treatment of Essential Hypertension";

Dr. David P. Barr, St. Louis, Mo.—A

Medical Diagnostic Clinic and an address, "The Significance of Jaundice";

Dr. Leonard G. Rowntree, Rochester,

Minn.—A Medical Diagnostic Clinic and an address, "Cirrhosis of the Liver";

Dr. Henry S. Plummer, Rochester, Minn.—

A Medical Diagnostic Clinic and an

address, "Cause of the Specific Phenomena of Exophthalmic Goiter";

Dr. Stewart R. Roberts, Atlanta, Ga.—An

address, "The Value of Tests for Liver Function";

Dr. Andrew C. Ivy, Chicago, Ill.—An ad-

dress, "Observation on the Etiology of Gall Stones."

At a meeting of the newly appointed State Board of Health of Florida, held in the Governor's office in Tallahassee, October 25, Dr. H. Mason Smith (Fellow), Tampa, was elected President of the Board.

Dr. Grayson E. Tarkington (Fellow), Hot Springs, Ark., is the author of an article on "Encephalography," appearing in the August issue of the Hospital Bulletin of the Levi Memorial Hospital.

Dr. Harold Swanberg (Fellow), Quincy, Ill., recently contributed his publication "Radium Therapy in Uterine Malignancy" to the College Library of publications by members.

At the eighty-third semi-annual meeting of the Southern California Medical Association at Long Beach, October 31—November 1, the following Fellows of the College gave addresses as indicated:

Dr. Noel F. Shambaugh, Long Beach

"The Dietary Factor in Kidney Disease"

Dr. Paul B. Roen, Los Angeles

"Senility—Cause and Prevention"

Dr. Arthur L. Bloomfield, San Francisco

"Indications for Use of Special Tests by the Practitioner"

Dr. Fred B. Clarke, Long Beach

"Chronic Meningococcic Septicemia"

Dr. Edward W. Hayes (Fellow), Monrovia, and Dr. John Dwight Davis (Fellow), Los Angeles, addressed the Los Angeles Trudeau Society, October 28, on "The Practical Application of the Recent Classification of Tuberculosis in Children" and "Pathologic Changes of Lymph Nodes in Experimental Tuberculosis," respectively.

Dr. Joseph A. Capps (Fellow), Chicago, used as the subject of his Presidential ad-



dress before the Chicago Pathological Society, October 13, "Pathogenesis of Cardiac Pain"

Dr Alexander A Goldsmith (Fellow), Chicago, addressed the Tri-County (Ill) Medical Society, October 13, on "Chronic Colitis"

Dr Albert Austin Pearre (Fellow), Frederick, Md, addressed the semi-annual meeting of the Medical and Chirurgical Faculty of Maryland at Westminster, October 22, on "Symptomatology of Hypothyroidism in the Adult"

Dr Philip S Hench (Fellow), Rochester, Minn, addressed the joint meeting of the Tenth Councilor District Medical Society and the Allegheny County (Pa.) Medical Society, October 21, on "Clinical Consideration of Chronic Arthritis" and "Recent Progress in Study and Treatment of Rheumatic Diseases"

At the annual meeting of the Oregon State Medical Society, held at Portland, Dr John H Fitzgibbon (Fellow), Portland, was elected a Vice President

Dr John Eiman (Fellow) and Dr Harold W Jones (Fellow), both of Philadelphia, were speakers at a symposium on the blood diseases, at the October 8 meeting of the Philadelphia County Medical Society

Dr William Egbert Robertson (Fellow), Philadelphia, delivered an address on "Discussion of the Principles Presented and their Relation to General Medicine" before the Philadelphia County Medical Society, October 22, which meeting was devoted to a discussion of "Recent Applications of the Fundamental Sciences to Certain Medical Problems"

Dr Samuel J Goldberg (Associate), Philadelphia, addressed the West End (Philadelphia) Medical Society, October 15, on bronchitis

The Norfolk County Medical Society was addressed on October 20 by Dr Walter B

Martin (Fellow), Norfolk, on "The Value of Iron in the Treatment of the Anemias"

Dr Otho A Fiedler (Fellow), Sheboygan, Wis., was made President-Elect at the annual meeting of the State Medical Society of Wisconsin on September 11

The thirtieth annual meeting of the Tenth District Medical Society, held at Eau Claire, Wis, was addressed by Dr Francis D Murphy (Fellow), on "Diabetes Its Complications and Its Management"

Dr Francis Eugene Senear (Fellow), Chicago, addressed the Medical Society of Milwaukee County, Wisconsin, October 10 His subject was, "Significance of Pruritus in Medicine"

Dr James Stuart Pritchard (Fellow), Battle Creek, journeyed to Newark, Ohio, October 2, in his monoplane to address the Eighth District Ohio Medical Society on "Significance of the Cough as a Symptom"

Dr Oliver T Osborne (Fellow), New Haven, Conn, is the author of an article entitled, "Thyroid Gland," syndicated by the Gorgas Memorial Institute throughout the United States on October 11

Dr Osborne is also author of an article on "Medical Education," which appeared in the Medical Journal and Record, October 1 Dr Osborne, furthermore, is author of several editorials which have appeared in recent issues of medical journals

Dr Sinclair Luton (Fellow) read a paper on "Recent Advances in the Study of Heart Diseases" before the Southwest Missouri Medical Society, Springfield, Missouri, November 6

Acknowledgment is made of the receipt of the following reprints, which have been properly indexed and added to the College Library of publications by members

Dr Samuel Goldberg (Associate), Philadelphia, Pa

1 Reprint—"Mesenteric Embolism in a Haemophilic"

Dr. Leo V. Schneider (Fellow), Baltimore, Md.

5 Reprints—"Laryngeal Tuberculosis"

"Undulant Fever of the Pseudotuberculous Type and Pulmonary Tuberculosis"

"Bilateral Pleural Effusion Inflammatory Type Following Pneumonia"

"Tuberculosis and Malignant Neoplasia"

Primary Aspergillosis of the Lungs"

Dr James Gurney Taylor (Fellow), Milwaukee, Wis, was a recent visitor to the College headquarters in Philadelphia

Dr Taylor has been elected a member of the National Board of Medical Examiners

Dr M M Canavan (Fellow), Curator of the Warren Anatomical Museum, Harvard University Medical School, has been granted leave of absence for three months, November 1, 1930, to February 1, 1931, for unofficial observations on medical conditions in Japan

Dr Henry Wallace (Fellow), New York, N Y, addressed the annual meeting of the Piscataquis County (Maine) Medical Society at Deer Island on Moosehead Lake, recently, concerning the all around work of the general practitioner far from the large centers, and made a plea for the return of the general practitioner in general

Dr. Clyde L. Cummer (Fellow), Cleveland, Ohio, was elected to membership in the American Dermatological Association at the recent annual meeting in Cleveland

Dr V C Rowland (Fellow), Cleveland, Ohio, is President of the Academy of Medicine of Cleveland

The following list of reprints, of which Dr Henry J John (Fellow), Cleveland, Ohio, is author, is duly acknowledged

"The Use of Intravenous Glucose in Diabetic Patients"

"The Importance of Early Diagnosis of Diabetes"

"Diabetic Coma"

"Diabetes"

"Diabetes"

"A Study of the Relation of the Blood Sugar in Plasma to that in the Corpuscles in Normal and Diabetic Individuals"

"Problems in Diabetes"

Dr R E Loucks (Fellow), Detroit, Michigan, is author of an article entitled, "Ten Years' Results with Radium in the Treatment of Toxic Goiter," published in the American Journal of Roentgenology and Radium Therapy

Dr Howard S Brasted (Fellow), Hornell, N Y, was recently appointed Examining Physician for the Civil Service Commission of Hornell

Dr H Lissner (Fellow and Governor for northern California is President of the California Academy of Medicine, a past President and a Councillor of the Association for the Study of Internal Secretions, and First Vice President of the San Francisco County Medical Society

Dr. Lissner is a contributor to the Biedl Festschrift-Endokrinologie 1929, Volume 5, Pages 138-170 article entitled, "The Unglandular Origin of Pluriglandular Syndromes" He is author of "A Further and Final Report on a Case of Tetanea Parathyreopriva treated for a year with Parathyroid Extract (Collip) with Eventual Death and Autopsy (with H Clare Shepardson, (M D), Endocrinology, September, 1929, Volume 13, Page 427 Also, "Recent Endocrinology," California and Western Medicine, Volume 33, Page 545-550, August, 1930

Lt Col Alexander T Cooper (Fellow), M C, U S A, retired September 29 as President of the Denver Sanatorium Association, being elected Honorary President.

Dr Robert G Douglas (Associate), Shreveport, La, addressed the Tri-County Medical Society of Arkansas, September 4, on "Diseases of the Colon."

At the Twentieth Annual Session of the American College of Surgeons at Philadelphia, October 17-17, the following Fellows of the American College of Physicians participated, as indicated below

Dr Orlando H Petty, Philadelphia—Ward Class of Diabetic Surgery

Dr George E Pfahler, Philadelphia—Exhibit of Technique and Results of Irradiation Treatment of Cancer of the Mouth,, Diagnosis of Bone Tumors, Radiation in the Diagnosis and Treatment of Malignant Disease

Dr H L Bockus, Philadelphia—Gastrointestinal Diagnosis

Dr George Morris Piersol—Cardiorenal Disease in Relation to Operative Risks

Dr O H Perry Pepper, Philadelphia (with George P Muller)—Exploratory Laparotomy in Face of Roentgenological Evidence of Pulmonary Metastasis

Dr Wilson A Myers (Fellow), Kansas City, spoke before the Jackson County (Mo) Medical Society, September 30, on "Spondylolisthesis with Special Reference to the Etiology and Pathology"

Dr Leonard G Rowntree (Fellow), Rochester, Minn, initiated a heart campaign sponsored by the Health Conservation Association of Kansas City, October 7, by an address on "Recent Advances in the Study of Heart Disease"

Dr Cyrus C Sturgis (Fellow), Professor of Medicine and Director of the Thomas Henry Simpson Memorial Institute for Medical Research of the University of Michigan Medical School, delivered the Middleton Goldsmith Lecture for 1930 of the New York Pathological Society at the New York Academy of Medicine on October 18, his subject being, "Recent Development in the Treatment of Pernicious Anemia and a Consideration of the Etiology of the Disease"

The program for the Third Annual Graduate Fortnight of the New York Academy of Medicine, October 20-21, featured medical and surgical aspects of acute bacterial infections. Among the speakers were

Dr Charles F Martin (Master), Montreal—"Continued Education of the Practitioner",

Dr E E Irons, (Fellow), Chicago—"Facts and Fancies Concerning Vaccines and Non-Specific Therapy",

Dr Emanuel Libman (Fellow), New York—"Acute and Subacute Bacterial Endocarditis",

Dr William W Herrick (Fellow), New York—"Meningococcus Infections, Including Meningitis"

Dr Hal M Davison (Fellow), Atlanta, addressed the Seventh District Medical Association of South Carolina, September 11, on "Neurosis in Internal Medicine"

Dr James Allison Hodges (Fellow), Richmond, addressed the Clinch Valley Medical Society, of Virginia, at its annual meeting, September 20, on clinical education

Dr Frederick G Banting (Fellow), Toronto, discoverer of insulin, was again honored on September 16 when the new \$800,000 Banting Institute of the University of Toronto was dedicated. Lord Moynihan, President of the Royal College of Surgeons of England, presided.

The new building replaces the old pathologic building of the University, and will combine its activities with the General Hospital. It is said that the cost of the building was contributed by the Provincial Government, the University and the Banting Research Foundation, which raised funds by popular subscriptions.

Dr Lyell C Kinney (Fellow), San Diego, addressed the San Diego County (Calif) Medical Society, October 14, on "The County Medical Society—A Business Organization"

Dr James G Carr (Fellow and Governor for northern Illinois), Chicago, (with Dr William C Danforth) addressed the McDonough County (Ill) Medical Society, October 14, on "Management of Pregnancy Complicated by Heart Disease"

Dr. Harry M Hedge (Fellow), Chicago, used as his subject "Modern Conceptions and Treatment of Syphilis" in a talk before the Rock Island County (Ill.) Medical Society, October 14.

Dr. I S. Trostler (Fellow), Chicago, spoke on "Roentgenotherapy of Conditions Other Than Cancer" before the McLean County (Ill.) Medical Society at Bloomington on October 14

During a two-day school for physicians, under the auspices of the Public Health Board of Evansville, Indiana, in early October, Dr Herman M Baker (Fellow), Evansville, was one of the speakers, his subject having been "Nontuberculous Diseases of the Lung"

Dr. Noel C Womack (Fellow), Jackson, Miss., addressed the Issaquen-Sharkey-Warren Counties (Miss.) Medical Society, September 9, on "Intracranial Hemorrhage in Infants"

Among speakers at the Northeast Mississippi Thirteen County Medical Society at Corinth, September 16, were Dr James S. McLester (Fellow), Birmingham, who spoke on the anemias, and Dr Felix J Underwood (Fellow), Jackson, who spoke on hospitals, nurses and health

At the twenty-seventh annual meeting of the Nevada State Medical Association at Reno, September 26-27, Dr De Los Schuyler Pulford, Jr (Associate), Woodland, Calif, spoke on "Benzol Poisoning a Report of a Case Simulating Anemia and Hemorrhagic Purpura", and Dr. Edward Matzger (Associate), San Francisco, Calif, spoke on "Seasonal Hay-Fever and Seasonal Asthma—a Preventable Disease."

"The Physician as Community Counselor" was the subject presented by Dr. James K Hall (Fellow), Richmond, Va, at the Ninth District (N C.) Medical Society on September 25.

Dr. John T Quirk (Associate), Piqua, Ohio, addressed the Miami County Medical

Society at Troy, Ohio, September 5, on "Diagnosis and Treatment of Pernicious Anemia"

Dr. Robert A. Knox (Fellow), Washington, Pa., spoke before the Washington County Medical Society, October 15, on "Hypertrophic Stenosis of the Pylorus"

Dr. Lester Hollander (Fellow), Pittsburgh, addressed the Fayette County (Pa.) Medical Society, October 2, on "Eczema and Ringworm"

At the Commencement Exercises of Union University, June, 1930, the degree of Doctor of Science was conferred on Dr. Hermon C Gordinier (Fellow), Professor of Medicine at the Albany Medical College

Dr James M Anders (Master) has been appointed Chairman of the Better Homes Committee of Philadelphia for the year 1930-1931 by Dr Wilbur, Secretary of the Interior, Washington, D C

Dr Willard C Stoner (Fellow), Cleveland, Ohio, addressed The Union Medical Association of the Sixth Councilor District at Kent, Ohio, on October 8, on "The Importance of an Intensive Program in the Treatment of Chronic Arthritis and Rheumatic Manifestations," and on October 20 he addressed The American Protestant Hospital Association at New Orleans on "The Increasing Cost to the Patient of Medical and Hospital Care"

#### COLLEGE MEMBERS MEET IN WESTERN PENNSYLVANIA

On October 25, Dr E Bosworth McCready, Governor of the American College of Physicians for western Pennsylvania, along with Dr Clement R Jones, Treasurer of the College, arranged a sectional gathering of all of the Fellows and Associates residing in western Pennsylvania. A dinner was held at the Duquesne Club in Pittsburgh, with the following Fellows present: Dr Syndey R Miller, President, Baltimore, Md., Dr George Morris Piersol, Secretary General, Philadelphia, Dr Clement R.

Jones, Treasurer, Dr E Bosworth McCready, Governor, Dr J M Thorne, Dr C C Hartman, Dr J. H Barach, Dr F. A. Evans, Dr R R Snowden, Dr. George W Grier, Dr Shaul George, Dr Henry M Ray, Dr Lester Hollander, Dr H. W Weurthele, all of Pittsburgh, Dr L D Sargent, Dr R A Knox, Dr G W Ramsey, all of Washington, Dr C C Campman, of West Middlesex, Dr H B Anderson, of Johnstown, Dr G H Hess and Dr E B Edie, of Umontown, and Dr W G Falconer, of Clearfield. In addition, the following Associates were present: Dr E M Frost, Dr H A Shaw, Dr Max Weinberg, all of Pittsburgh, Dr G F Stoney, of Erie, Dr G A Ricketts, of Osceola Mills. Mr E R Loveland, the Executive Secretary from Philadelphia, was also present, as were also eleven invited guests.

Governor McCready and Treasurer Jones made appropriate remarks concerning the activities of the College in western Pennsylvania. Mr Loveland spoke briefly of the business organization and operation of the College. Secretary General Piersol spoke at length concerning the standards of the College with respect to admission and the work of the Committee on Credentials. President Miller acted as Toastmaster, giving at the end an inspiring address concerning the whole field of activity for the College and outlined the laudable objects the College should accomplish. The meeting contributed much to the enthusiasm and understanding of the members of the College, as well as promoted good fellowship generally. This was the second sectional gathering held during the past few months by members of the College, the previous one being the Fellows and Associates of the College in the State of North Carolina. The effects of these sectional gatherings are far-reaching and inspiring, and should be encouraged throughout all parts of the country.

### THE COLLEGE LIBRARY

#### *Have You Contributed?*

Two years or more ago, the Board of Regents conceived the idea of establishing a library of books of which its members are the authors. The library, in a sense, is intended to be a Memorial Library to its mem-

bers. A general medical library, other than one composed of publications by the members, would scarcely be justified in the College headquarters, both due to inadequate housing facilities and lack of availability to members. However, there are ample facilities for a library of all of the books that have been published by Fellows of the College, and such a library is of considerable value and great interest.

It is regretted that comparatively so few of the members have actually contributed their books. Reprints have been submitted in profusion, and are gratefully received, but a library of mere reprints does not approach in interest a library of books. Fellows of the American College of Physicians constitute a group of probably the most productive medical men of America. Books of which they are authors are not only numerous, but occupy a forefront position in American medical literature.

Your contributions should be sent to the Executive Secretary, Mr E R Loveland, 133-135 S 36th Street, Philadelphia, Pa., who will promptly acknowledge their receipt, both to you personally and in the columns of the *Annals of Internal Medicine*. They will then be properly indexed, both by title and author's name, and placed on the bookshelves in the reception room of the College.

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Dr Herbert W Rathe (Associate), Waverley, Ia, "Coronary Disease with Special Reference to Acute Coronary Accidents, Their Recognition and Treatment"

Dr Charles N Hensel (Fellow), St Paul, Minn, "Nonmyxedematous Hypothyroidism"

Dr Moses Barron (Fellow), Minneapolis, "Treatment of Bright's Disease"

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At the annual meeting of the Medical and Surgical Association of the Southwest at El Paso, Texas, November 6-8, the following Fellows were scheduled to deliver addresses indicated:

Dr George R Herrmann, New Orleans, illustrated lectures—"Diagnostic Criteria of Heart Disease" and "Treatment of Syphilitic Aortic Disease in the Last Stages",

Dr. Roy E. Thomas, Los Angeles, "Management of Lobar Pneumonia",

Dr. Walter C. Alvarez, Rochester, Minn., "Practical Points in Treatment of Gastro-Intestinal Disease",

Dr. LeRoy S. Peters, Albuquerque, "Cauterization of Adhesions—Jacobaeus—Unverricht Method".

Dr. Edward Matzger (Associate), San Francisco, addressed the San Francisco County Medical Society, August 12, on "Studies in Human Hypersensitiveness—Recent Advances"

Dr. James K. Fancher (Associate), Atlanta, Ga., addressed the Fulton County Medical Society, August 7, on "The Influence of Sodium Cacodylate on the Leukocyte Count"

At the 80th annual session of the Kentucky State Medical Association, held at Bowling Green, September 15-18, Dr. Oscar O. Miller (Fellow), Louisville, delivered an address on "Present-Day Conception of Pulmonary Tuberculosis in Infancy and Childhood"

Dr. Emmet F. Horine (Fellow), Louisville, delivered the oration in medicine on "Mechanism of the Heart Beat"

The annual meeting of the Southern Minnesota Medical Association, August 25, at Mankato, was addressed by the following members of the College

Dr. Walter C. Alvarez (Fellow), Rochester, Minn., "The Art of Medicine"

At the eighth annual fall clinical conference of the Kansas City Southwest Clinical Society, held in Kansas City, October 6-10, Dr. Leonard G. Rowntree (Fellow), Rochester, Minn., and Dr. Ralph C. Matson (Fellow), Portland, Oregon, were guests speakers.

Dr. Oliver P. Kimball (Fellow), Cleveland, addressed the Portland City and County Medical Society at Portland, Ore., July 16, on "Relation of Thyroid Disease to Mental Deficiency".

Dr. Jack Witherspoon (Fellow), Nashville, Tenn., addressed the Northeastern Division of the Alabama State Medical Association, June 24, on duodenal ulcer.

Dr. Herman N. Bundesen (Fellow), Chicago, was one of the speakers at a symposium on crime detection, August 27-30, conducted by the Scientific Crime Detection Laboratory and Northwestern University

Dr. Louis M. Warfield (Fellow), Milwaukee, addressed the 110th annual meeting of the Michigan State Medical Society at Benton Harbor, September 15-17, on "Tachycardia"

At the meeting of the Eastern Oregon District Medical Society, August 27, Dr. John H. Fitzgibbon (Fellow), Portland, delivered a paper on "Occlusion of the Fallopian Tubes", and Dr. Marr Bisailon (Fellow), also of Portland, gave a paper on "Pulmonary Tuberculosis"

Dr. Frank Howard Richardson (Fellow), Black Mountain, N. C., and Dr. Horton R. Casparis (Fellow), Nashville, Tenn., addressed the Spartanburg County Medical Society (South Carolina), July 28, on "Posture in Children" and "Causes of Infant Mortality During First Year of Life", respectively

Dr. Aldred Scott Warthin (Master) Ann Arbor, Michigan, addressed the 36th annual meeting of the Utah State Medical Association at Salt Lake City, September 9, on "The Newer Therapeutic Attack on Cancer"

The same meeting was addressed by Dr. Andrew C. Ivy (Fellow), Chicago, on "Observation on the Cause of Gallstones", by Dr. William Gerry Morgan (Fellow), Washington, D. C., on "Some Observations on Etiology", and by Dr. William S. Thayer (Fellow), Baltimore

At the annual meeting of the American Protestant Hospital Association at New Orleans, October 17-20, among the sched-

uled speakers appeared the following Fellows of the College

Dr John H Musser, New Orleans, "Interns",

Dr Willard C Stoner, Cleveland, "The Increasing Cost of Medical and Hospital Care"

Dr Christopher G Parnall (Fellow), N Y, was the guest of honor at the annual banquet

Dr Joseph G Terrence (Associate), Brooklyn, N Y, was recently elected to the

Presidency of the Brooklyn Society of Internal Medicine

Dr Judson Daland (Fellow), Philadelphia, has just returned from visiting South America, where he was studying the diseases peculiar to that Continent

Dr Edgar Erskine Hume (Fellow), Major, Medical Corps, U S Army, who has been Medical Inspector of the Infantry School at Fort Benning, Georgia, was transferred to Boston on October 1 Dr Hume was the recipient of the degree LL.D from the University of Kentucky last June

### SOUTHERN MEDICAL ASSOCIATION MEETING

The Southern Medical Association held its twenty-fourth annual meeting at Louisville, Kentucky, November 11-14, 1930 Members of the American College of Physicians occupied one hundred and twenty-four distinct assignments Among the more important, the following are mentioned

Dr Hugh S Cumming (Fellow), Washington, as President,

Dr Walter E Vest (Fellow), Huntington, Dr Morgan Smith (Fellow), Little Rock, Dr William Gerry Morgan (Fellow), Washington, Dr Sydney R Miller (Fellow), Baltimore, Dr W McKim Marriott (Fellow), St Louis, Dr Lea A Riely (Fellow), Oklahoma City, and Dr Alfred L Gray (Fellow), Richmond, as Councilors,

Dr Stewart R Roberts (Fellow), Atlanta, Dr C C Bass (Fellow), New Orleans, and Dr William R Bathurst (Fellow), Little Rock, as members of the Board of Trustees

Among those occupying offices on various sections are the following

*Section on Medicine*—Dr C W Dowden (Fellow), Louisville, Chairman

Dr T Z Cason (Fellow), Jacksonville, Vice Chairman

*Section on Pediatrics*—Dr H Leslie Moore, Dallas, Chairman

Dr Philip F Barbour (Fellow), Louisville, Host

*Section on Gastro-Enterology*—Dr G W F Rembert (Fellow), Jackson, Chairman

Dr Elmer B Freeman (Fellow), Baltimore, Secretary

Dr Charles G Lucas (Fellow), Louisville, Host

*Section on Neurology and Psychiatry*—Dr R Finley Gayle, Jr (Fellow), Richmond, Chairman

Dr Charles S Holbrook (Fellow), New Orleans, Vice Chairman

Dr William E Gardner (Fellow) and Dr John J Moren (Fellow), both of Louisville, Hosts

*Section on Medical Education*—Dr Robert Wilson (Fellow), Charleston, Chairman

Dr Russell H Oppenheimer (Fellow), Atlanta, Vice Chairman

Dr Kenneth M Lynch (Fellow), Charleston, Secretary

Dr John Walker Moore (Fellow) and Dr Virgil E Simpson (Fellow), both of Louisville, Hosts

Among Fellows of the College offering scientific exhibits were the following

Dr W W Duke (Fellow), Kansas City, Mo, offered a scientific exhibit showing various causes and effects of allergy, methods of study, methods of diagnosis and treatment, and methods of preparation of material for diagnosis and treatment

Dr Charles N Kavanaugh (Fellow), Lexington, gave a scientific exhibit on Tularemia—color photographs of lesions, gross and microscopic

Dr Emmet F Horne (Fellow), Louisville, moving pictures of the mechanism of cardiac action

Dr W W Anderson (Fellow), Atlanta, photographs of clinical conditions in children

On the General Session, Dr Emmet F Horne (Fellow) gave the Presidential Address of Welcome in behalf of the Jefferson County Medical Society Dr Hugh S Cumming (Fellow), Surgeon General of the U S Public Health Service and President of the Southern Medical Association, gave the annual Presidential Address on "Future Relations of the Profession to the Public" Dr M W Ireland (Fellow), Surgeon General of the U S Army, gave the oration on surgery, "The Relation of Internal Medicine and Surgery" Dr Alfred Stengel (Master) Professor of Medicine at the University of Pennsylvania School of Medicine, gave the oration on medicine, "Empiricism and Science in Medical Practice"

At the General Clinical Sessions, the following contributed, as indicated

Dr John J Moren (Fellow), Louisville, "Post-Encephalitic Phenomena, Parkinsonian Type",

Dr William E Gardner (Fellow), Louisville, "Jamaica Ginger Paralysis",

Dr Philip F Barbour (Fellow), Louisville, "Anemia of the Newborn",

Dr Oscar O Miller (Fellow), Louisville, "New Methods in the Management of Chronic Tuberculosis",

Dr Allen H Bunce (Fellow), Atlanta, "Differential Diagnosis of Abdominal Conditions";

Dr Stewart R Roberts (Fellow), Atlanta, "The Heart in Pregnancy",

Dr John H Musser (Fellow), New Orleans, "The Blood in Disease"

In the Section on Medicine, the program was offered almost wholly by Fellows of the College We list the following who offered papers, but omit the names of discussants

Dr C W Dowden (Fellow), Louisville, Chairman's Address,

Dr Cyrus C Sturgis (Fellow), Ann Arbor, "The Treatment of Pernicious Anemia",

Dr J E Knighton (Fellow), Shreveport, "Melanomatosis with Case Report",

Dr J Heyward Gibbes (Fellow), Columbia, S C, "The Results of Agglutination Tests for Undulant Fever",

Dr W W Duke (Fellow), Kansas City, "New Aspects of Gastro-Intestinal Allergy",

Dr C H Cocke (Fellow), Asheville, "The Healing of Tuberculosis"

To the Section on Pediatrics, the following contributed papers or clinics

Dr Philip F Barbour (Fellow) and Dr James W Bruce (Associate), Louisville, a Clinic

Dr H Leslie Moore (Fellow), Dallas, "A Clinical Observation in Nutritional Injuries",

Dr Fritz B Talbot (Fellow), Boston, "Endocrine Disturbances in Childhood",

Dr Ray M Balyeat (Fellow), Oklahoma City, "Manifestations of Allergy in Children",



- Dr C C McLean (Fellow), Birmingham, "Periodical Seasonal Incidence of Gastro-Intestinal Symptoms Complicating Respiratory Infections in Childhood",
- Dr W McKim Marriott (Fellow), St Louis, "Enteral and Parenteral Factors in the Causation of Diarrhea",
- Dr Carroll M Pounders (Fellow), Oklahoma City, "Appendicitis in Children from the Pediatricist's Point of View"

In the Section on Gastro-Enterology, again members of the College contributed a large portion of the program

- Dr G W F Rembert (Fellow), Jackson, Chairman's Address on "Gastro-Enterology An Important Phase in Diagnostic Procedure",
- Dr Walter C Alvarez (Fellow), Rochester, "Some Practical Points in the Treatment of Gastro-Intestinal Diseases",
- Dr Daniel N Silverman (Fellow), New Orleans, "Bacterial Forms of Dysentery in the South A Clinical and Bacteriological Study",
- Dr Jack Witherspoon (Fellow), Nashville, "Spastic Constipation",
- Dr L C Sanders (Associate), Memphis, "Carcinoma of the Colon A Plea for Early Diagnosis",
- Dr Julius Friedenwald (Fellow) and Dr Theodore H Morrison (Fellow), Baltimore, "Some Observations on the Secondary Gastric Disturbances Occurring in Pulmonary Tuberculosis",
- Dr Seale Harris (Fellow), Birmingham, "The Dietary Management of the Ulcer Patient Before and After Operation",
- Dr John B Fitts (Fellow), Atlanta, "Cancer of the Stomach in the Southern Negro A Study of Fifty Cases"

To the Section on Pathology, Dr Aldred Scott Warthin (Master), Ann Arbor, delivered an illustrated paper on "The Pathology of Latent Syphilis"

To the Section on Neurology and Psychiatry, the following contributed papers

- Dr R Finley Gayle, Jr, (Fellow), Richmond, Chairman's Address, "The Relationship Between Neurology and General Medicine and Surgery",
- Dr Walter Freeman (Fellow), Washington, "Malaria Therapy in Private Practice"

To the Section on Radiology, Dr W P Baker (Fellow), Atlanta, contributed a paper on "Observations Based Upon the Treatment of Six Hundred Cases with Deep X-Ray Therapy"

To the Section on Public Health, Dr O C Wenger (Fellow) of the U S Public Health Service, Hot Springs National Park, contributed a paper on "The Incidence of Syphilis in the Negroes of the South"

To the program of the National Malaria Committee, Dr Engene R Whitmore (Fellow), Washington, contributed a paper on "Plasmochin in Malaria"

To the Section on Medical Education, the following contributed, as indicated

- Dr Robert Wilson (Fellow), Charleston, Chairman's Address on "Aims and Methods in Education",
- Dr James S McLester (Fellow), Birmingham, "The Teaching of Therapeutics",
- Dr Charles T Stone (Fellow), Galveston, "Levels of Nursing The Practical Nurse, the Trained Nurse, the Specialized Nurse, and Their Relations to the Economics of Illness",
- Dr W S Leathers (Fellow), Nashville, "The Responsibility of the Medical School in the Education of the Nurse"

## OBITUARY

Dr William Burley Bowman (Fellow), Los Angeles, Calif, died, October 20, 1930, of heart disease

Dr Bowman was born at Martin's Ferry, Ohio, in 1885. He received his medical training at St Louis University School of Medicine, from which he graduated in 1910. He went to Los Angeles soon after graduation, and established hospital connections as Attending Roentgenologist to the California Lutheran and St Vincent's Hospitals and at the University of California Postgraduate Clinic. He early limited his efforts to X-Ray work, in which field he became one of the outstanding men in the community. His earnest endeavor in the field of Roentgenology and his efforts in the fields of constructive medicine made him widely known.

At the time of his death, he was attending Roentgenologist to the Santa Fé and Methodist Hospitals, Consulting Roentgenologist to the Children's and General Hospitals and to the Barlow Sanatorium. He was a member of the Alpha Kappa Kappa Fraternity, the Los Angeles County Medical Society, the American Roentgenological Society, the California State Medical Society, the Clinical and Pathological Society, the American Association of Military Roentgenologist and a Fellow of the American Medical Association. He had been a Fellow of the American College of Physicians since April 3, 1922. His sudden death was a shock to his friends and colleagues everywhere.

—Furnished by Egerton L. Crispin, M.D., F.A.C.P., Governor for Southern California

Dr Murrett Fauquier DeLorme (Fellow), Brooklyn, N. Y., died September 8, of heart disease, aged 61 years.

Dr DeLorme was born at Sumter, North Carolina. He attended the University of Maryland, Department of Pharmacy, from which he received the degree of Ph.G. He then attended the Bellevue Medical College during the years 1896-1897; thence he transferred to the Long Island College Hospital from which he received the degree of Doctor of Medicine in 1900. At the Long Island College Hospital, Dr DeLorme was Instructor in Pharmacy and Materia Medica from 1900 to 1903, from 1903 to 1906, Lecturer in Pharmacology, from 1907 to 1915, Assistant Professor in Materia Medica and Pharmacology, and since 1916, had been Clinical Professor of Medicine.

Dr DeLorme numbered among his publications the following: "A Manual of Pharmacy for Physicians," in three editions, published by P. Blakiston's Sons and Co.; "A Syllabus of Materia Medica," published by J. C. Lindsay Co.; and "An Experiment in the Application of Diabetic Dietetics," published in the Journal of the American Medical Association.

He was a Fellow of the American Medical Association, a member of the Medical Society of the County of Kings, a member of the Medical Society of the State of New York, a member of the Associated Physicians of Long Island and a member of the Society of Internal Medicine of Brooklyn. He was among the original group who met at the Hotel Astor, New York, in 1915 to formulate plans for

the founding of the American Congress on Internal Medicine, but did not become a Fellow of the American College of Physicians until 1928. He was an active member of the College, enthusiastic about its policy and objects.

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Dr Herman C Gordinier (Fellow), prominent physician, and a specialist on lung and heart disease, died last month at his home at 89 Fourth Street, Troy, New York. He had been ill for a long time. Dr Gordinier was 66 years old. He was born in Troy, May 21, 1864, and always resided here, where he studied and built up his lucrative practice. He was educated in the public schools and was graduated from the Albany Medical College in 1886. Subsequently he took a course at the University of Prague in Austria.

For more than 40 years he was a Professor in the Albany Medical College, where he was noted for his thoroughness. He was one of the founders and a member of the Board of Trustees of the Samaritan Hospital, where he served as a physician and neurologist. He was also a physician at the Mary McClellan Hospital at Cambridge.

He was an instructor in physical diagnosis in the Albany Medical College from 1889 to 1895, after which he became a Professor of Anatomy and Physiology and finally Professor of Medicine. Dr Gordinier received a number of honorary degrees, including Master of Arts from Williams College and Doctor of Science from Union College.

He was a member of numerous societies, including the Rensselaer

County Medical Society, the New York State Medical Society and the American Medical Association. He was also an honorary member of the American Neurological Society, the American Physicians Society, the American Therapeutic Society, the New York Academy of Medicine and the American College of Physicians. For many years he held offices in all the organizations.

He was a member of the Troy Club, the Troy Country Club, the Troy Riding Club, Mount Zion Lodge, F and A M, and the Scottish Rite Societies. He was a Director of the Union National Bank.

Dr Gordinier contributed a number of articles to medical books and magazines. During his early days he published a catalogue on "Flora and Fauna of Rensselaer County." He was the author of a number of books on nervous diseases.

Dr Gordinier's death removes one of the city's noted citizens and one of the best physicians in this part of the country. He is survived by two daughters, Miss Hermione Gordinier and Mrs George P Ide, 2d, one son, Hermon C Gordinier, all of this city, and a brother, Adam Gordinier of Schenectady.

The funeral was held Wednesday afternoon at 2 30 o'clock from St John's Episcopal Church. Rev Dr Henry R Freeman, rector emeritus of St John's Church, officiated. Interment was in Oakwood Cemetery.

Mayor Burns paid the following tribute to Dr Gordinier:

"The passing of Dr Hermon C Gordinier removes from our city one of its most distinguished native citi-

zens. As a physician, he was a leader, commanding the respect and admiration of his professional colleagues. As a man and a friend he was known to thousands, who had for him the utmost confidence and regard.

"During his years of professional life, Dr Gordinier gave unceasingly and unselfishly of his time and talents to administer to those who needed him. Devotion to duty, and love for his fellow beings were his motives, rather than the idea of monetary reward in hundreds of cases where his patients could ill afford to pay. No personal sacrifice was too great if, because of it, someone benefited.

"As a professor of medicine at Albany Medical College he passed on to

those entering the profession much of the knowledge which had placed his name in the fore in medical circles in the nation.

"Dr Gordinier brought to his native city a high honor, for he was more than a loyal physician and his fame extended far. As Mayor of the city which reflected his glory, I voice the regrets of its people at his death. Personally, I counted Dr Gordinier as a friend, and to have been was an honor of which anyone can justly be proud.

"Dr Gordinier will be missed and his place will be most difficult to fill. But those who mourn him will find solace in the knowing that he has gone on to the reward which he so well earned."

# Diagnostic and Physiologic Studies in Certain Forms of Scleroderma\*

GEORGE E. BROWN, M D, *Division of Medicine,*  
PAUL A. O'LEARY, M D, *Section on Dermatology and Syphilology,*  
and

ALFRED W. ADSON, M D, *Section on Neurologic Surgery,*  
THE MAYO CLINIC, Rochester, Minnesota

**S**CLERODERMA is the term that has been applied to a syndrome characterized by induration, pigmentation, and sclerosis of the skin, associated with loss of weight, asthenia, arthritis, atrophy of muscles and other symptoms, depending on the degree and extent of the hidebinding. Cases of the disease may be divided into two groups: the diffuse or generalized form, and the localized form known as morphea or circumscribed scleroderma. The group known as morphea will be eliminated from this report.

The onset of the diffuse form of scleroderma varies. It may be ushered in with symptoms of arthralgia, malaise, loss of weight, and asthenia, or it may develop acutely following systemic infection, frequently interpreted as influenza; other cases have been observed to follow, and seem definitely related to, acute arsenism. Among the most frequently observed cases are those in which the scleroderma starts insidiously and pursues a slow, pro-

gressive course, and in which there is no discernible etiology. The cases, with which this paper is chiefly concerned, are composed of the patients in whom evidence of Raynaud's disease is associated with the scleroderma (Table I).

The dermatologic features of the disease are the same, irrespective of the mode of onset, hence it is impossible to classify the disease from its clinical appearance. However, the distribution may give a clue as to the mode of onset, that is often confirmed by the history. The etiology of scleroderma is unknown, so that our classification of the disease according to the mode of onset was adopted as a means of grouping the cases from the standpoint of therapeutics rather than from that of etiology. In the literature may be found a variety of explanations and hypotheses with regard to the etiology of scleroderma, and for detailed material the reader is referred to the article by Boardman who recently thoroughly reviewed the literature. The present conception of the etiology of scleroderma may be summarized briefly in the statement that a variety of noxae have been

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\*Read before the American College of Physicians, Minneapolis, Minnesota, February 10 to 14, 1930.

TABLE I  
GROUP I PRIMARY SCLERODERMA, VASOMOTOR DISTURBANCE APPEARED AFTER THE SCLERODERMA WAS WELL DEVELOPED

Case	Age, years, and sex	Duration of disease, months	Duration of vasomotor disturbances	Duration of sclerodermal changes	Extent of sclerodermal changes	Disability and progression	Classification of cases
1	37 M	15	One month, slight color changes	Fifteen months, swelling in hands, one year, in duration	Face, neck, hands and arms	Rapid progression for six months, 75 per cent disability	Primary scleroderma, short duration, severe form
2	41 M	18	One year, cyanosis of hands with cold	Eighteen months, progressive stiffening of skin of hands	Fairly generalized, most marked in hands, arms, face	Progressive weakness, rapid increase in induration of skin, 75 per cent disability	Primary scleroderma; short duration, severe form
3	30 M	24	Eighteen months, cyanosis of hands with cold	Twenty-four months, swelling of hands, then hardening of skin	Hands, arms, face and neck, partial fixation of joint	Marked weakness, muscular atrophy, pigmentation, graded 390 per cent disability	Primary scleroderma, short, rapid course

recognized as factors in the production of the disease, and that one or several of these noxae may be involved in a given case. Among the outstanding causes may be cited infections, arsenism, trauma, vasomotor diseases in the extremities, and dysfunction of the glands of internal secretion, particularly of the thyroid gland.

Watson, in 1754, reported the first case, as quoted in detail by Willan in 1808. In 1895 Lewin and Heller reviewed a series of 508 cases, and three years later Osler reported a series of eight cases, in one of which the history was that of a syndrome resembling Raynaud's disease which preceded the onset of the scleroderma and sclerodactylia. The Raynaud-scleroderma syndrome has been recognized repeatedly since, and has been the basis for the conception that scleroderma is attributable to vasomotor neurosis, angioneurosis, or angiotrophoneurosis. Cassirer recognized the relationship to vasomotor disease, and divided scleroderma into three types: the Raynaud type, the vasomotor type without gangrene, and the typical form, in which, late in the disease, Raynaud symptoms with gangrene develop. We have modified this classification slightly and group the cases of the vasospastic type of scleroderma with sclerodactylia into those in which the sclerodermal process has been the primary disturbance (table 1), and vasomotor disturbances, which are often absent, appear, if at all, relatively late, those cases (table 2), in which the vasomotor disturbances appear simultaneously with the onset of the sclerodactylia, and those in which the vasospastic disturbance precedes the appearance of the scleroderma or

the sclerodactylia by months or years (table 3).

In a clinical study of 103 cases of scleroderma, O'Leary and Nomland found that in 33 per cent of the cases of generalized scleroderma there was a definite history of vasomotor phenomena in the extremities preceding the onset of the sclerodactylia. The severity of the vasomotor symptoms in this group was variable, ranging from moderate cyanosis on exposure to cold, to the more severe cases, in which were all the evidences of typical Raynaud's disease, with the white, blue, and red stages, and the accompanying pain. In cases of the vasomotor type, the scleroderma manifested itself first in the hands (sclerodactylia) and gradually extended up to the arm, the face and upper part of the thorax, and sometimes the feet, were involved simultaneously. It is not to be inferred from this that sclerodactylia is solely a manifestation of the vasomotor type of the disease, because O'Leary and Nomland noted sclerodactylia in 89 per cent of the cases with the generalized type of the disease. The five cases (11 per cent) in which there was no involvement of the hands, did not present evidence of vasomotor disease of the extremities.

The vasomotor type of this disease may readily be distinguished from the other varieties, not only from the history of the vasospastic disease, but also from the characteristic distribution, in which the hands, forearms, face, upper part of the thorax (fig 1) and feet are primarily involved. This distribution is to be contrasted with other types of generalized scleroderma in which the trunk and face may show the

TABLE 2

## TYPE 2 SIMULTANEOUS DEVELOPMENT OF SCLERODERMA AND VASOMOTOR DISTURBANCES\*

Case	Age, years, and sex	Duration of disease, months	Duration of vasomotor disturbances	Duration of sclerodermal changes	Extent of sclerodermal changes	Disability and progression
4	50 F	18	Eighteen months, pallor, and cyanosis of hands with cold	Seven months, stiffening of skin of hands, face and neck, with intermittent swelling of feet	Generalized, except back of thorax, fixation 50 per cent in fingers, dry ulcers of knuckles	75 per cent in upper extremities
5	55 F	24	Twenty-four months, cold hands and cyanosis with swelling of fingers	Twenty-four months, swelling in hands, six months rapid progression of scleroderma in face and arms	Upper extremities, face, neck and thorax	Mild weakness, disability 30 per cent in hands
6	19 F	24	Twenty-four months, pallor, numbness and swelling of fingers	Twenty-four months, swelling in hands, twelve months hardening of skin in hands, cyanosis with cold	Hands, arms, face and thorax, mild in feet	Mild weakness, about 30 per cent disability in hands
7	34 M	42	Forty-two months, pallor, cyanosis, numbness, stiffness of skin in hands	Forty-two months, numbness and stiffness in hands, six months rapid progression of induration of skin	Hands, arms, face, neck and thorax, feet and lower legs, painful joints and muscular atrophy	70 per cent disability in hands, painful joints and muscles

\*All of these cases were classified as of the rapidly progressive form, with vasomotor symptoms appearing with the onset of scleroderma



TABLE 3  
GROUP 3 VASOMOTOR DISTURBANCES PRECEDING DEVELOPMENT OF SCLERODERMA

Case	Age, years, and sex	Duration of disease, years	Duration of vaso-motor disturbances	Duration of sclero-dermal changes	Extent of sclero-dermal changes	Disability and progression	Classification of cases
8	24 M	5	Five years, blanching and cyanosis in hands with cold, recurring ulcers	Six months, stiffness in skin of hands	Hands, and in feet	90 per cent in hands	Localized form of scleroderma in acral areas
9	32 F	5	Five years, attacks of pallor and cyanosis in hands with cold and nervousness, one year, same in feet	Three years, stiffness in hands, ulcers one year in feet	Hands, arms, face, neck and feet	50 per cent in feet, 80 per cent in hands, mild weakness	Chronic vasomotor form
10	35 F	5	Five years, pallor and cyanosis, and pain in hands with cold	Three years, ulcers and induration of skin of hands, painful	Hands and face	75 per cent in hands	Chronic vasomotor form
11	31 M	8	Eight years, changes of color in hands and feet	Seven years, mild stiffness of fingers and face	Hands, with ulcers, slight in face	75 per cent in hands, mild weakness	Chronic vasomotor form
12	35 F	11	Eleven years, blanching and cyanosis in fingers with cold	Ten years, swelling, ulcers of fingers, gradual progressive scleroderma	Hands, arms, thorax and face (?)	60 per cent in hands	Probably a vasomotor form, slowly progressive scleroderma

TABLE 3 (Continued)  
TYPE 3 VASOMOTOR DISTURBANCES PRECEDING DEVELOPMENT OF SCLERODERMA

Case	Age, years, and sex	Duration of disease, years	Duration of vaso-motor disturbances	Duration of sclero-dermal changes	Extent of sclero-dermal changes	Disability and progression	Classification of cases
13	37 F	13	Thirteen years, pallor and cyanosis in fingers, six years, same in feet	Three years, dry ulcers of hands	Hands and face (?), feet cyanotic	75 per cent in hands	Chronic vasomotor form
14	44 F	15	Fifteen years, changes of color in hands with cold	Ten years, ulcers of finger, pain graded 3	Generalized on hands, face, neck and thorax, feet in stage of swelling	75 per cent in hands, weakness, mental irritability	Chronic vasomotor form
15	57 F	17	Seventeen years, changes of color in hands, five years, same in feet	Ten years, stiffness of hands, flexion deformities	Generalized, least in feet	50 per cent in hands, weakness, graded 2	Chronic vasomotor form.
16	25 F	22	Twenty-two years, cyanosis and pallor in hands, feet, and skin of body	Nineteen years previously sclerodermal changes appeared, continued with vaso-motor disturbance	Generalized, worse in hands and arms	Scleroderma regressive in last years, almost disappeared in face	Chronic vasomotor form, regressive on body, loss of fingers from ulcers

greater degree of involvement, with the sclerodactylia absent or appearing as a late manifestation

### MATERIAL

This report concerns clinical and physiologic studies, and evaluation of surgical treatment, in sixteen cases of scleroderma in which vasospastic disease of the extremities was present. When the time of development of the vasomotor factor in relation to the appearance of the scleroderma was considered, three groups were recognized: (1) nine cases in which the vasomotor condition was primary, (2) four cases in which the sclerodactylia and the vasospasm appeared simultaneously, and (3) three cases in which the vasomotor disturbance developed after the appearance of the sclerodactylia. In all cases the skin of the hands was affected chiefly, but that of the arms, face, and thorax, and of the lower extremities, was involved in some degree. There were six men and nine women, with ages ranging from nineteen to fifty-seven years. The duration of the disease varied from one to twenty-two years. Several of these patients, when first seen, had the characteristic symptoms and signs of Raynaud's disease, without induration of the skin, but at subsequent observations the scleroderma was found to be well developed. In all of these cases, the scleroderma had progressed far enough to have produced atrophy of the appendages of the skin (figs 2, 3, 4, and 5) with trophic ulcers of the fingers and regions of the knuckles, or of the extensor surfaces of the elbows. In case 9, the disease was present in a fairly early stage in the feet, probably representing

the first stage or the stage of swelling, whereas in the hands the process was well advanced. Pigmentation was present in some degree in every case, and in one case to a degree to be confused with Addison's disease (fig 6). In Case 16, a period of regression of the scleroderma in the skin of the face, arms, and thorax had taken place, and the sole residue was the vasospastic disturbance of the fingers, melting ulcers of the finger tips, gangrene, and repeated symmetric amputation of the fingers.

### HISTOLOGIC PATHOLOGY

The study of the pathologic changes in the skin in scleroderma has not thrown light on the etiology of the disease. Conversely, inadequate knowledge of the etiology makes it difficult to interpret the pathologic changes observed, not only those in the skin but also those found in the viscera at necropsy.

Ormsby has summarized the cutaneous pathologic changes in a well established case as being characterized by hypertrophy of the collagen, comparative absence of blood vessels, large numbers of dilated lymph spaces, hyperpigmentation both in the rete and the corium, and comparative absence of the glands of the skin. A variety of opinions has been recorded in regard to the relationship of these various pathologic processes, however, it seems agreed that the hypertrophy of the collagen results in phenomena due to pressure that interferes with the blood supply. The effects of pressure, and the local anemia, lead to atrophy of the appendages of the skin.

The reported observations at necropsy in cases of scleroderma are not

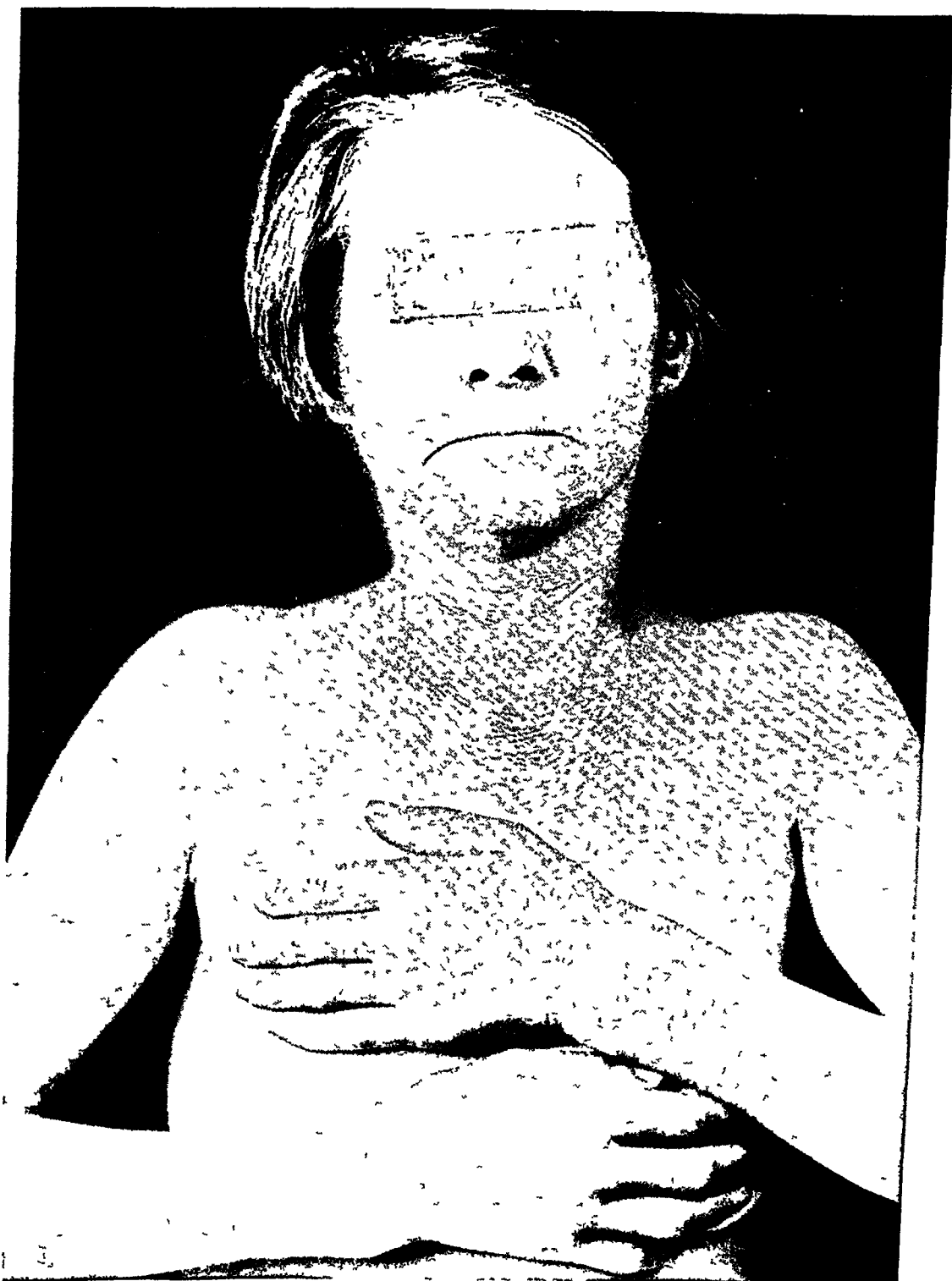


FIG 1 The distribution of the cutaneous changes in an early case of the vasomotor type of scleroderma



FIG 2 Mild form of sclerodactylia

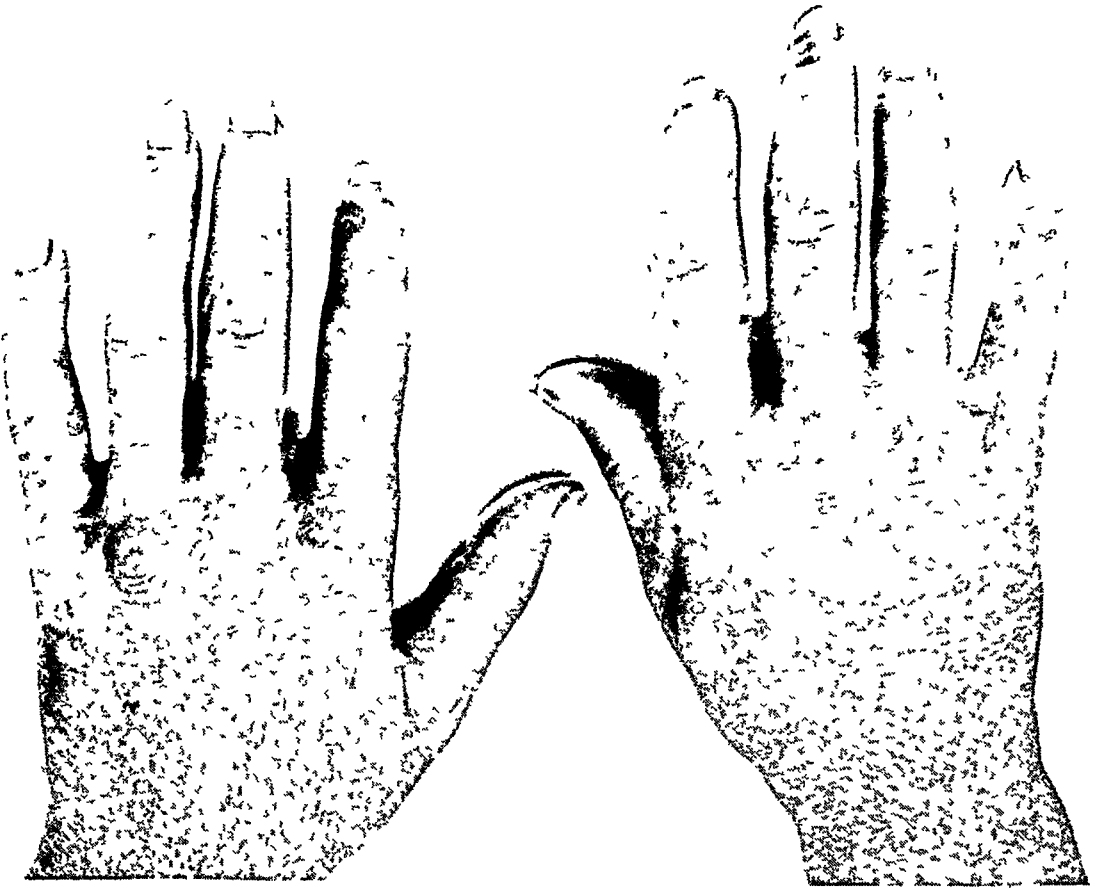


FIG 3 Sclerodactylia of more severe form than that shown in Figure 2

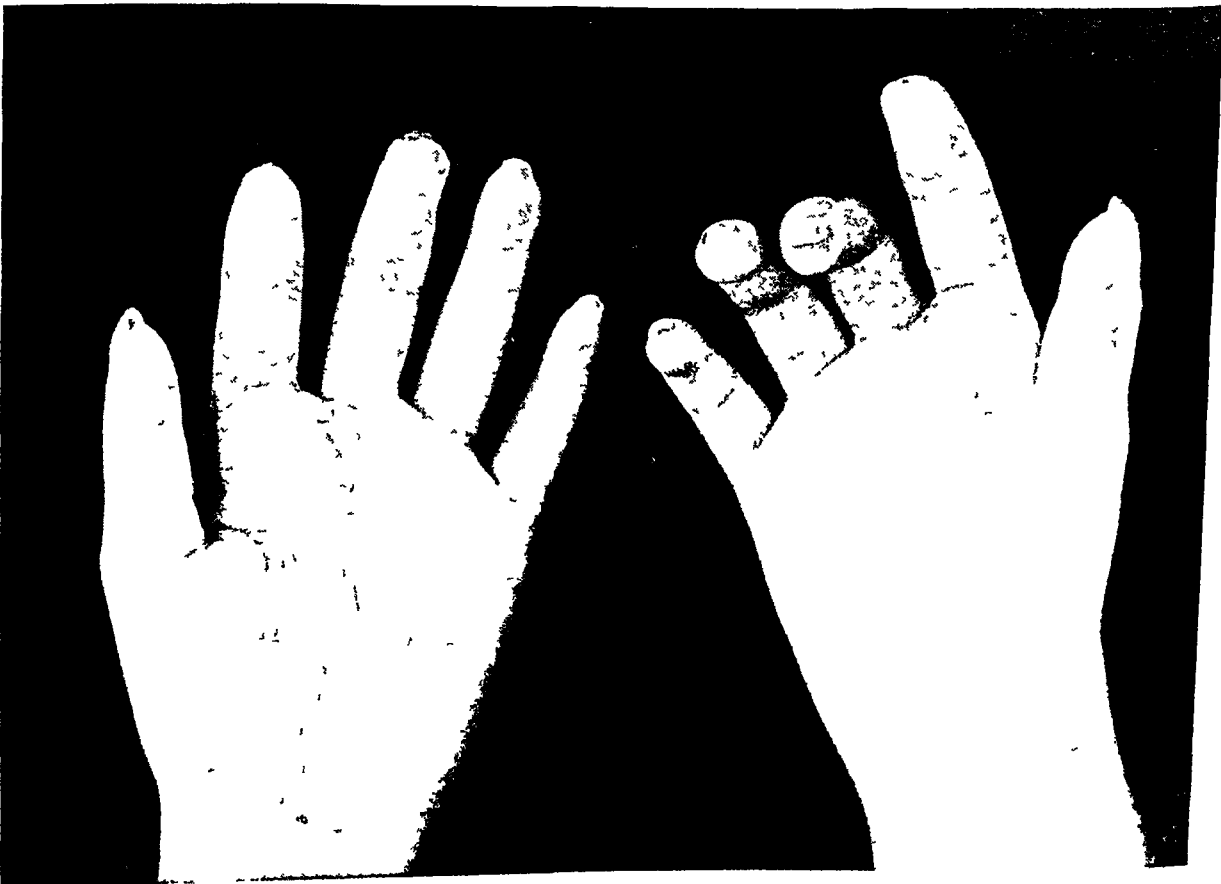


FIG 4 Severe form of sclerodactylia, with destruction of terminal phalanges



FIG 5 Trophic ulcers in the vasomotor type of sclerodactylia

numerous, but the six reports of cases made by Matsui are detailed. He stated that not only was there proliferation of the collagen in the skin and changes in the small, cutaneous arteries, but that similar changes were noted in certain of the viscera. These degenerative changes were in the lungs, kidneys, and endocrine glands. He studied the glands of internal secretion in detail and felt that, as a result of the changes noted, the etiology of scleroderma was attributable to endocrine dysfunction. We have studied sections of skin in advanced cases of the diffuse type, as well as from patients with the vasomotor type, and the changes are considerably similar, they differ, however, in the fact that in the latter type there is considerably more cellular infiltration, both within and around the small vessels of the skin. A detailed consideration of the significance of the cellular reaction is not possible, but this reaction is so common and pronounced that it suggests the possibility that the vascular changes are forerunners of some of the other pathologic features. It also seems justifiable to attribute the changes in the thyroid gland, in which sclerosis has been noted at necropsy, as the result of the systemic involvement, rather

than the cause of it. Particularly significant is the cellular infiltrate around and in the smaller blood vessels in the acute edematous phase of the disease, before the collagen deposits are well organized.

#### PHYSIOLOGIC PATHOLOGY

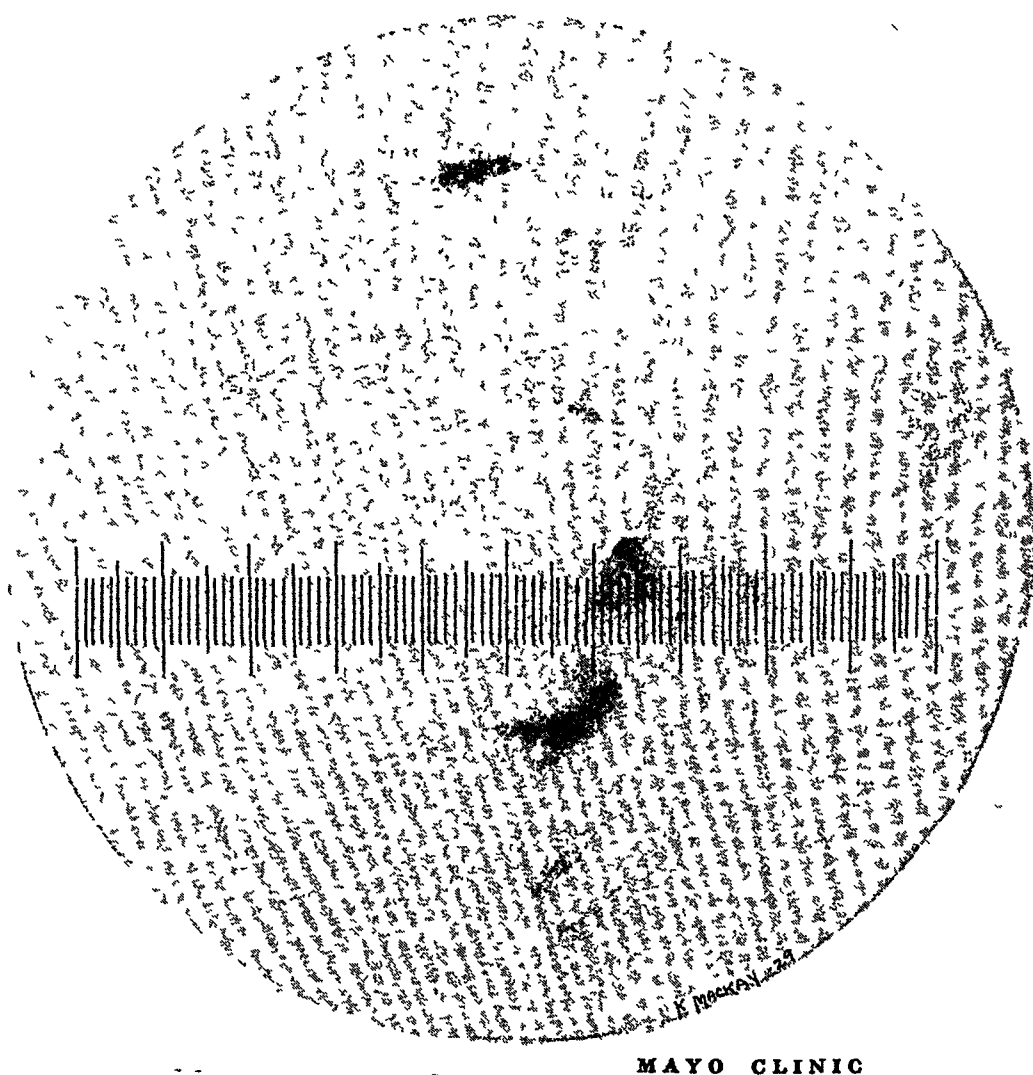
*Surface Capillaries* Microscopic studies of the capillaries in the nailfold had been made previous to the time of this study by Brown and O'Leary. Similar studies have been made in all of these sixteen cases, and the significant changes were found to be sharp diminution in the number of open capillaries for each unit area of skin, and reduction to approximately a half or a third of the normal number. The capillaries, in this condition, are large, distorted, and irregular (figs 7 and 8), and frequently one capillary of this type may be the only one seen in the field. The outlines of the capillaries are frayed, irregular, indistinct and appear as irregular masses of blood. The flow of blood through the loops is markedly disturbed. With slight lowering of the environmental temperature, the flow becomes slowed or stationary. The blood becomes deeply cyanotic in color, and with higher environmental or bod-



MAYO CLINIC

FIG 6 Pigmentation of the hand severe enough to resemble Addison's disease, in the vasomotor type of scleroderma





MAYO CLINIC

FIG 7 (Case 5) Capillaries of the nailfold before operation

ily temperature there is acceleration of the rate of flow, with transition to a reddish color. Marked impairment in the transparency of the skin is usual, which makes it extremely difficult to define the outlines of the loops. This is due probably to three factors: (1) the increased density in the skin, (2) perhaps the interference with the flow of lymph and accumulation of fluid, and (3) the pigmentation.

The most striking impression gained from examination of the capillaries is

the great reduction in the amount of circulating capillary blood in the skin. These changes explain the reduced temperature and the pale color of the skin. The marked susceptibility to slowing of the capillary flow with slightly reduced temperature, and the changes in color, reflect the exaggerated tonus of the arterioles. The excessive sweating of the hands of many patients also indicates excessive stimulation of the sympathetic apparatus. The changes in the surface capillaries



FIG 8 (Case 5) Capillaries of nailfold after operation

emphasize the fact that the major factor in a well advanced case is the lack of blood in the skin. This lack of blood is due to two factors: the increase in the collagen, which results in obliteration by pressure of the arterioles and capillaries, and an excessive degree of vasospasm in the arterioles. The determination of the magnitude of the vasomotor element will be considered later.

*Surface Temperature* Determinations of surface temperature have been

carried out in the hospital under fairly constant conditions of environmental temperature. The skin of the hands or feet of a patient with sclerodactylia is usually cold and clammy, has a cadaveric appearance and the temperature of the hands and feet is lower than that of the surrounding air. In a normal subject, the average surface temperature of the fingers, as determined with the thermocouple, in a room in which the temperature is maintained at a range of  $24^{\circ}$  to  $26^{\circ}$  C, ranges between

32° and 35° C. In these cases, it varied from 19.6° to 29.8° C, averaging about 25.3° C (fig 9). In the earlier vasomotor forms of scleroderma, the temperature of the skin of the hands and feet may vary within a wide range. At times, the hands and feet are excessively cold, again, warm or even hot. This is further evidence of excessive hypertonus of the arterioles.

**Rates of Elimination of Heat** In the hands and feet the rates of elimination of heat have been studied with the Stewart and Kegerreis calorimeter. This method, as explained by Sheard and by Brown<sup>4</sup>, determines, over a fixed period of time, the amount of heat eliminated from the limb and taken up by a given volume of water in which the limb is immersed. The loss of heat is expressed as small calories of heat eliminated from the entire hand for each minute of time. The rate of elimination of heat for the normal

hand averages about 100 small calories for each minute. This method of study is probably the best procedure for determining, in an indirect way, the volume flow of blood through the extremities, and constitutes an extremely valuable method for the comparative studies to determine the effects of treatment on volume flow of blood.

The mean value for nine cases of scleroderma was 34 small calories of heat eliminated for each minute (fig 10). All had rates of loss of heat considerably less than normal. There was no significant difference in the values for the different forms of scleroderma included in this study.

**Vasomotor Indexes** A method for determining quantitatively the amount of vasospasm in the extremity has been devised by Brown<sup>5</sup>. This method determines the so-called vasomotor index, which indicates the increase in surface temperature of the foot or hand for

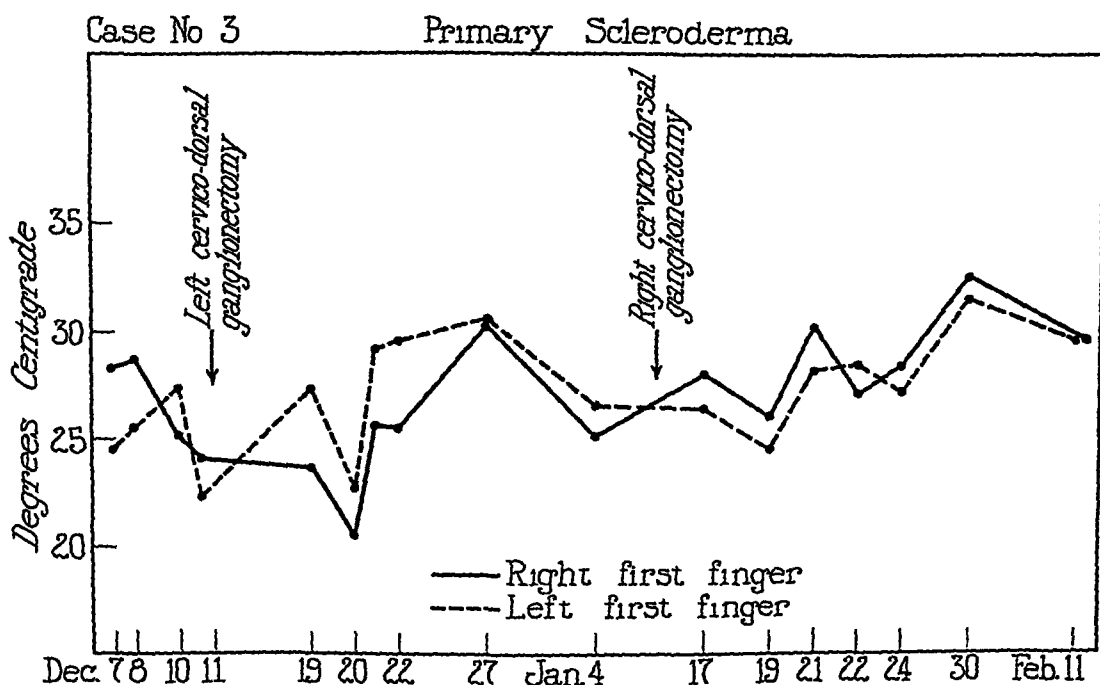


FIG 9 (Case 3) Studies of surface temperature, before and after operation

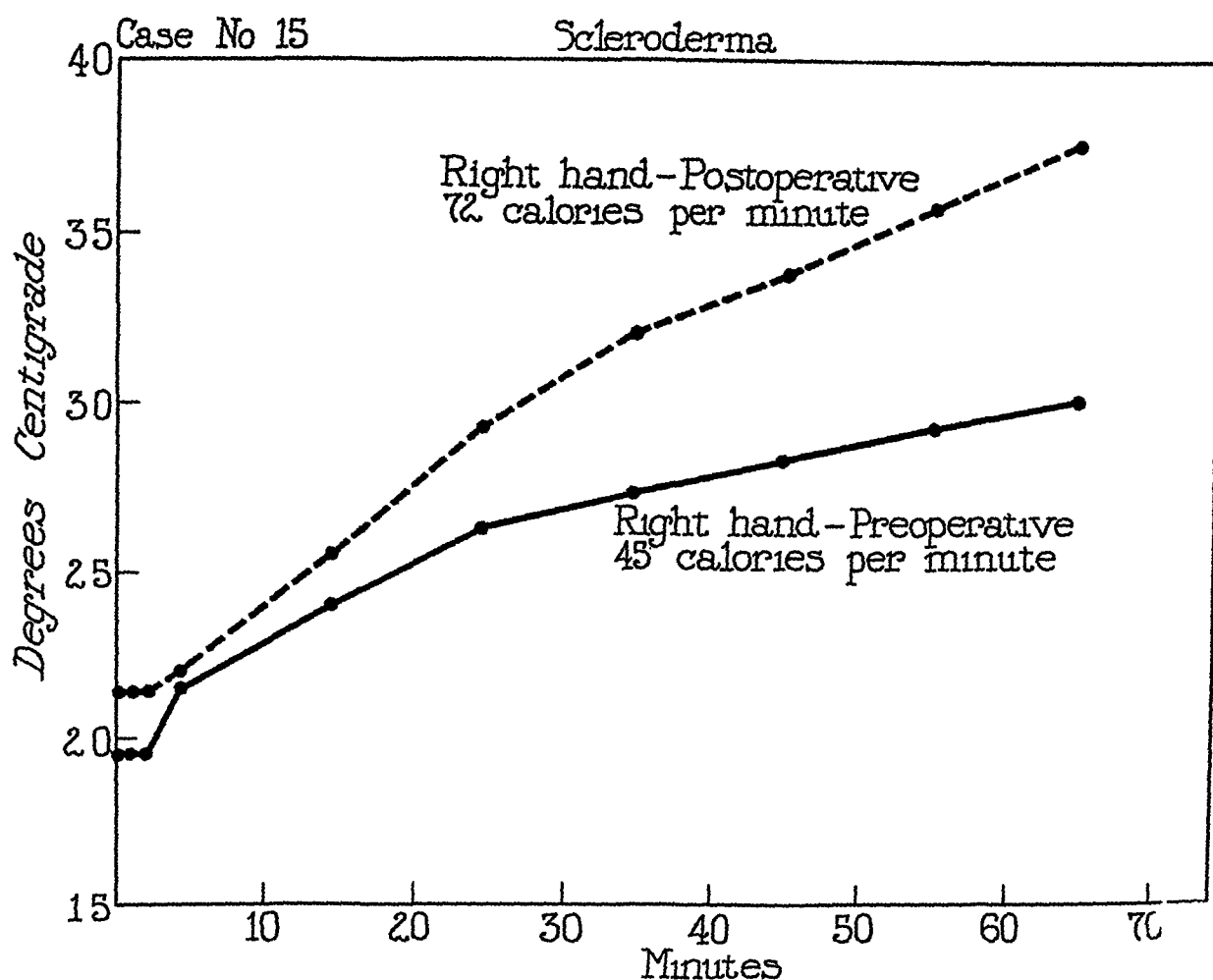


FIG 10 (Case 15) Curve of elimination of heat before and after operation

each degree of temperature of the body. In vasomotor disturbances of the spastic type, for example in Raynaud's disease, high indexes are obtained, frequently the value is 10 or more. In normal subjects, with warm hands or feet, low indexes are obtained. With occlusive disease of the arteries, such as thrombo-angitis obliterans, wide variations are obtained, varying from less than 1 to 8. This is evidence that in some cases, with occlusive disease of the arteries, the lower temperature of the skin is due not solely to occlusion of the main arteries but also to the additional factor of an excessive amount of vasospasm in the collateral arteries and arterioles. The test is carried out as follows. The patient is given foreign protein (typhoid vaccine) intraven-

ously, the surface temperatures of the hands and feet are estimated, and simultaneously the temperature of the mouth is recorded. During the period of chill there may be a fall in the surface temperature, but with the rise in the temperature of the mouth there is relaxation of the surface vessels and rapid increase in the temperatures of the skin, the difference between the maximal rise in the surface temperature and the maximal increase in blood (mouth) temperature constitutes the rise in surface temperature due largely to vasomotor effects. This value, divided by the number of degrees rise in temperature in mouth or blood, gives a value which, simply stated, represents the increase, in number of degrees, in the surface temperature for each de-

gree of increase in temperature of the body

In cases of scleroderma it has been found that vasomotor indexes varied from 27 to 138, with an average value of 65. In the vasomotor forms of scleroderma, as a whole, there are slightly higher indexes than in the other forms of scleroderma (fig 11). The indexes are not as high as those in cases of Raynaud's disease. This is to be expected, for reduction in cutaneous circulation in Raynaud's disease is due exclusively, we believe, to spasm. In scleroderma, there is the additional factor of occlusive disease of the smaller arterioles.

#### CLINICAL COURSE

The clinical course of three phases of scleroderma, with vasospastic disease of varying degrees, is presented in the following reports of cases.

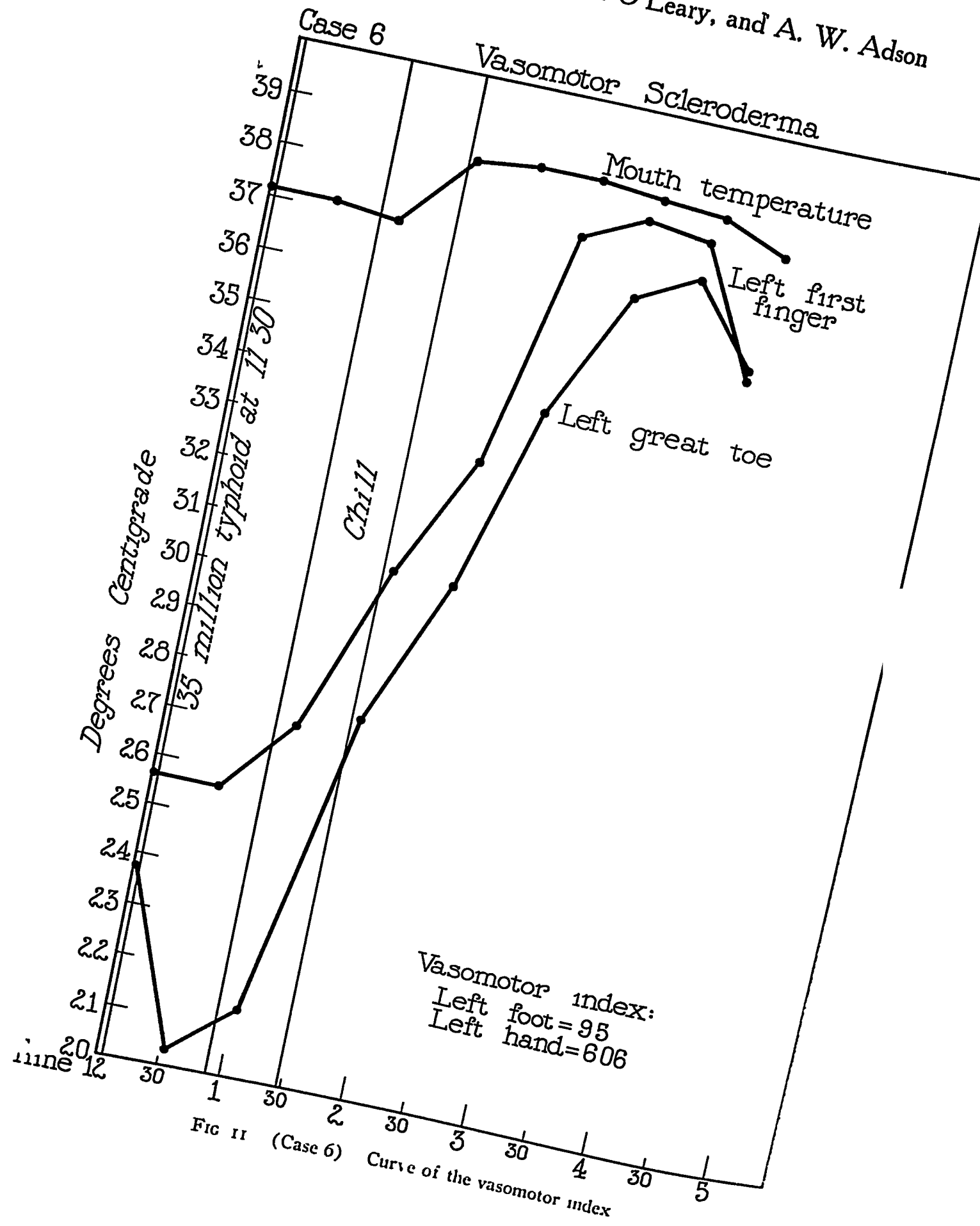
*CASE I (case 3, table 1, type 1), sclerodactylia followed by symptoms of vasospastic disease*—A man, aged thirty years, a machinist, came to The Mayo Clinic November 26, 1928. He had had the usual children's diseases, and had had erysipelas when he was aged fifteen years. Otherwise he had been well. In September, 1928, he had had pleurisy on the left side, and occasionally he had had pain on deep breathing. He had lost 16 pounds since the onset of the disease. Nothing was elicited in his family history or personal habits that was significant. In February, 1927, he had noted that his fingers were swollen and puffy in the morning. The swelling gradually had disappeared an hour or two after he rose from bed and his hands had remained normal until the following morning when the same course had repeated itself. Six months after the onset, the swelling had become constant during day and night, and had remained constant for several months. When the swelling had begun to subside, the patient had noted that his fingers were hard and stiff, so that he had been unable to clench his fist. This hardening of the skin

gradually had increased and had extended up the arm. At this time, about nine months after onset, he also had noticed that the fingers were sensitive to cold and when exposed to cold became blue. He was quite certain that they had not become white and only rarely had displayed a reddened phase. In December, 1927, about ten months after the trouble had appeared, he had noticed a similar process developing in the feet, and later in the face.

A diagnosis of Raynaud's disease had been made elsewhere in September, 1928, and treatment by roentgen rays had been given over the back, in addition to contrast mineral baths and "electric baths." In October, 1928, right cervical sympathectomy had been done elsewhere, following which his condition had not been improved.

When the patient was examined at the clinic the face was without wrinkles, had a waxy hue and imparted a sensation of firmness to the touch. Over the zygoma, the skin was so tight that it was impossible to "pick it up" like normal skin. The trunk, arms, and legs were hyperpigmented, some of the pigmentation, however, was the result of treatment by ultra-violet light. All the fingers were cold, waxy, stiff and smooth, and the skin seemed firmly attached to underlying structures. The skin of the palms was more flexible. The fingers were moderately flexed and could not be fully extended nor fully flexed. The skin of the forearm, and up to the lower third of the arm, also was thickened, firm, and waxy, but to a less degree than that of the hand. The toes appeared cyanosed and the skin of them was not so thickened as that of the arms. The blood vessels in both feet were patent. Examination of the thorax revealed a friction rub over the base of the left lung, otherwise the results of general examination were within normal limits. The blood pressure was 120 systolic and 75 diastolic, in millimeters of mercury, and the ocular fundi appeared to be normal. The tonsils were only slightly enlarged and contained plugs of inspissated pus.

Analysis of the urine and the blood count gave normal results. The Wassermann reaction of the blood was negative. Two apically infected teeth were demonstrated.



Roentgenologic examination of the hands disclosed partial destruction of the terminal phalanx of the right thumb, and of the thorax, nothing abnormal. The basal metabolic rate (DuBois standard) was  $+12$  per cent. The electrocardiographic report contained notations of sinus rhythm, aberrant QRS complexes, isolated derivation I, slurred right ventricular preponderance and a cardiac rate of 80 beats each minute. The vasomotor index in the right hand was 5.9, and in the left, 8.5. The surface capillaries were large and deformed, with a slow flow of cyanotic blood, typical of true scleroderma. The surface temperature in the right hand was  $27.1^{\circ}\text{C}$  and in the left,  $24.6^{\circ}\text{C}$ . Elimination of heat was estimated at 70 calories each minute.

A diagnosis was made of scleroderma with sclerodactylia and secondary vasomotor characteristics, for which resection of sympathetic ganglia and trunks was recommended.

December 11, 1928, Adson performed this operation in the left cervicothoracic region, and included the lower cervical and the two upper thoracic ganglia and the intervening trunk. It was thought advisable to postpone resection on the right side until the near future. When the patient was examined twenty-four hours after the operation, the left hand was warm and dry, but the right was unchanged. A Horner's syndrome was present on the left side. The second day after the operation, the skin of the left hand was decidedly softer than that of the right, and was of normal pink color. The veins on the left hand were fuller than those on the right and the color did not change materially with change of position. Definite parasthesia of the left arm was present.

January 8, 1929, a similar operation was performed on the right side, when the patient was ready for dismissal from the hospital, January 28, 1929 (seven weeks after the resection on the left side and three weeks after resection on the right), it was noted that the facial expression was different. The patient could wrinkle the forehead, pucker the mouth, and whistle much more readily. The sensation imparted to the fingers when palpation about the mouth was carried on was that the skin was loose rather than tight, as previously. The skin over the fingers was still stiff, although that on the fore-

arm and back of the hand was looser. There was no change in the mobility or flexibility of the hand. Hyperesthesia of both arms was still present, and considerable difficulty was encountered in the healing of the wound in the skin due to the influence of previous treatment by roentgen rays and of the sclerodermatous skin.

The result of the operation on this patient has not been satisfactory. Eight months after operation, he reported, by letter, considerable edema and pain in both upper and lower extremities.

CASE II (case 4, table 2, type 2), *sclerodactylia and vasospastic disease appearing simultaneously*—A woman, aged fifty years, who worked as a charwoman, came under our observation in October, 1929, because of stiffness of the extremities. The remote history was irrelevant. She had three healthy children. She had undergone uneventful menopause three years before she came to the clinic. The essentials of her brief story were as follows. Approximately one year before we saw her she had noticed that her fingers became blue when they were exposed to cold but rapidly assumed the normal color when they were warmed. There had been no white or red stage and no pain of significance. About six months later she had noted swelling of the fingers and lower part of the legs, which was followed by stiffness of the skin of the hands and fingers. Approximately one month later, a similar sensation had appeared in the skin about the lower part of the face and neck, and also in the feet and lower half of the legs. Since then there had been gradual increase in the "stiffness" of the skin involved and extension up the arms and down over the shoulder girdle. Almost simultaneously with the onset of the scleroderma, numbness had developed in the fingers, associated with blanching and pain. Hyperpigmentation of the sclerodermatous areas had appeared three months before admission.

When the patient was examined, she seemed considerably younger than her years. Her face was almost wrinkleless and there was some decrease in the palpebral fissures. Ability to protrude the tongue was limited, due to restricted mobility of the jaw. The skin of the lower half of the face was

"tighter" than that of the upper half. The hands were held in a semiflexed position. Some healing excoriations were noted over the knuckles and the finger tips. The veins of the hands were not visible, and the hands were cold, wet, and "hard." The skin of the arms was firm and that over the upper part of the thorax had the characteristic sheen of scleroderma. The feet and legs also gave evidence of scleroderma of a less marked degree. Neurologic examination gave negative results.

The blood pressures were 110 systolic and 78 diastolic. Comparison of the patient's weight with what she said it formerly had been disclosed that she had lost 30 pounds since the onset of the disease. The urine appeared to be normal and studies of the blood disclosed mild secondary anemia. Roentgenologic examination of the thorax gave negative results. The basal metabolic rate (Du Bois standard) was +6 per cent. The vasomotor index of the right index finger was 81, of the right great toe, 6, and of the left great toe, 58. Elimination of heat in the right hand was 21 calories each minute, the surface temperature was 24.4° C in the right hand and 26° C in the left.

A diagnosis was made of scleroderma, with sclerodactylia and mild vasoplastic disease appearing simultaneously. Resection of sympathetic ganglia and trunks was recommended.

October 15, 1929, Adson performed bilateral resection of cervicothoracic sympathetic ganglia and trunks.

Convalescence was uneventful, and on dismissal from the hospital, October 24, the patient reported that her hands were decidedly warmer, the skin over the backs of the hands was looser and the hyperpigmentation was fading. However, she complained of numbness in both arms, which had persisted since the operation, and she was unable to open her mouth as wide as she had been able to open it previous to the operation. She presented a bilateral Horner's syndrome. Three months later she reported that the color of the hands was normal but they were still stiff. Her main difficulty was dryness of the throat, increase in stiffness of the feet and some residual numbness in the arms.

CASE III (case 15, table 3, type 3), *vasoplastic disease preceding the development of sclerodactylia*—An unmarried woman, a school teacher, aged forty-eight years, came under our care for the first time in June, 1922. She came with a diagnosis of Raynaud's disease. In 1912, periods had appeared during which the left ring finger was numb and there was definite blanching of the finger. The frequency of these attacks had increased, and soon other fingers had been involved. By 1917, five years after the onset of the disease, on exposure to cold all the fingers and toes first became white and cold, then blue, and finally red and warm. During this developmental period, the patient had noted that her fingers were becoming stiffer, a condition which was called to her attention particularly while she was dressing her hair. By 1920, the fingers had become stiff and "wooden-like", involvement of the feet was much less. The patient emphasized the fact that the changes in color, and later on the stiffness in the fingers, both had been much worse during the cold weather. The stiffness of the skin of the face and thorax first had been noticed by the patient in 1921. During this developmental period a variety of therapeutic measures had been tried. Because a basal metabolic rate of +2 per cent had been noted in 1921, thyroid extract had been given, and in the spring of 1922, when the basal metabolic rate had been reported as -26 per cent, thyroid extract and thyroxin had been given until the rate had been raised to -11 per cent. As this had caused palpitation and precordial distress, the medication had been stopped, although the patient had felt somewhat improved. The use of ergot, suprarenal extract, pituitary extract anterior lobe, and nitroglycerine she said also had made her feel worse. During the year previous to admission to The Mayo Clinic she had noted that on exposure, such as that caused by undressing in a cold room, her skin had become blue and mottled, in irregular areas, and then flushed when she had become warm.

The patient was thin, with a pinched expression of the mouth. Although palpation of the skin of the face revealed little evidence of scleroderma, there was definite ironing out of wrinkles, and limitation of opening of the mouth. The skin over the thorax had a



definite sheen suggesting a slight degree of atrophy, but there was no palpable thickening. There was definite mottling of the skin of the trunk. The extremities, the hands in particular, were most markedly involved. The hands appeared waxy, the fingers were stiff and permitted of about 25 per cent flexion. The joints of the fingers were enlarged and tender to pressure. It was impossible to pick up the skin over the phalanges, although on the backs of the hands this could be accomplished with some limitation. The hands were cold and moist. A similar condition of the feet was noted, but to a much less degree. Also, palpable plaques, varying in size up to 5 mm, were noted along the peroneal tendons. When the fingers were exposed to cold water, or when they were hanging, they became cyanosed. The urine appeared to be normal. Secondary anemia was present as was shown by a concentration of hemoglobin of 67 per cent. Other factors of the blood count were within normal limits. The Wassermann reaction of the blood was negative. The basal metabolic rate (DuBois standard) was  $-7$  per cent. The retinal vessels were tortuous, but otherwise the ocular fundus was normal. The search for foci of infection disclosed slightly enlarged and infected tonsils, and six teeth with apical infection. The cardiovascular and pelvic examinations disclosed normal conditions. The vasomotor index was not done but the surface temperature was  $26.6^{\circ}\text{C}$  in the right hand, and  $27.9^{\circ}\text{C}$  in the left.

It was suggested that the foci be removed, and that the patient continue with massage, following application of dry heat to the hands.

The patient returned for reexamination in 1926, four years after her first visit. Besides the original complaint, the chief trouble at this time was difficulty in swallowing, this was found to be due to a benign stricture of the esophagus, about 37.5 cm from the central incisors. Vinson dilated the stricture frequently, and after prolonged observation he believed that it was not related to the scleroderma. At the time of the patient's second visit, the changes in the hands and face were more marked. The skin over the fingers and face was tighter, there was less motion in the fingers, and the patient was not

able to open her mouth as wide as before because the skin of her face was stiffer. Also, the joints of the fingers caused more pain, and rheumatism in the shoulders had developed. Roentgenologic examination revealed periarticular arthritis, with marked contraction deformity of the fingers. During the interval of four years since the patient's first visit to the clinic, she had received numerous intravenous injections of sodium thiosulphate without benefit. She had been treated also by the application of roentgen rays, massage and heat. Thyroid extract had been given and foci of infection had been removed but her condition had not improved. The similarity of the condition to Raynaud's disease was recognized at this time, and cervical resection of sympathetic ganglia and trunks was suggested, but was refused by the patient.

The following year, 1927, she returned, primarily for the esophageal stricture. There was no improvement in the scleroderma. In 1929, however, a decided increase in the severity and extent of the sclerodermatous involvement was noted. The degree of periarticular arthritis was more pronounced, in addition, roentgenograms disclosed atrophy of the bones of the hands. Small deposits of calcium also were noted in the finger tips. On the arms and upper part of the thorax there was now palpable hardening of the skin, the changes in color remained about the same.

June 18, 1929, bilateral resection of cervico-thoracic sympathetic ganglia and trunks was performed by Adson. On the seventh day after operation, a decided change in the facial expression was noted, the normal pink hue had replaced the previous waxy appearance, and the skin was decidedly softer. There was slight change in the capillary reactions over the anterior part of the thorax at this time. Horner's syndrome was present and equal on both sides.

On the fifteenth day after operation, the skin of the fingers, up to the first joints, was normal in appearance. All of the fingers were warm, but the mobility was not increased. The patient remarked that the "feeling of deadness and cold" had entirely disappeared. The tongue could be protruded further because the mouth could be opened

wider. The capillary reactions over the face and thorax had approached normal. The orbital fissures opened equally, but both pupils were contracted (Horner's syndrome).

A recent communication from the patient, seven months after the operation, stated that she had gained 10 pounds and that the most gratifying thing to her was that even though she was in a cold climate her hands had remained warm on the coldest days. The softening of the skin of the hands, which was noticed to a slight degree immediately after the operation, had continued to become more noticeable. Also the skin of the face and neck was much softer and had continued to improve. A number of superficial hemangiomas that had been present on the neck and upper part of the thorax also had disappeared. The only postoperative discomfort was pain in the right shoulder which developed after the arm was used for any length of time. She noticed it particularly after writing on the blackboard in her school work. Her hands were also "slippery" as a result of the extreme dryness.

#### PROGNOSIS

The expectancy of life of a patient with the generalized type of scleroderma is fairly long, not infrequently twenty years. The vasomotor type of the disease is likewise of long duration. We have not had the opportunity to study a case of scleroderma at necropsy and the literature contains but few data on observations at necropsy. The cause of death in scleroderma may be a terminal vascular disease or, more frequently, some intercurrent infection.

#### MEDICAL TREATMENT

There is no satisfactory medical treatment for generalized scleroderma. Because so many agents have been thought to be etiologic, the treatment has been varied. In the generalized type, thyroid extract has long been recommended. It is probable that the re-

lief obtained from the administration of thyroid extract is due to the vasodilating effect of the drug rather than to any specific influence on the thyroid gland. The use of massage following the application of heat has offered some help. In the group of cases reported by O'Leary and Nomland, only 6 per cent were materially benefited by treatment, in spite of the varied treatment. In a certain group of patients with the generalized form of the disease, there is spontaneous involution of the indurated skin, however, rather typical thin, atrophic scarring remains. This must be continually borne in mind in appraising the end-results in the treatment of scleroderma by any method. These few remarks on the inadequacy of treatment apply to the vascular type as well as to the diffuse forms of scleroderma. In those patients who are able to move to a dry, equable climate, such as that offered by the extreme southwestern part of this country, and who continue with massage, contrast baths, and supportive measures, the disease is of slower progress.

#### SURGICAL TREATMENT

*Theoretic Bases for Resection of Sympathetic Ganglia and Trunks in Cases of Vasomotor Type of Scleroderma*—Clinical and thermometric observations convince us that sympathetic hypertonus of the arterioles is a significant element in the diminished vascularity of the skin in at least one group of cases of scleroderma. Whether or not the vasomotor disturbance is the primary agent in this type of case is not known. Much experience with this disease has convinced us that in this disorder the stage before the scler-

derma is marked by vasomotor disturbances which simulate Raynaud's disease. This disturbance may antedate for years the onset of organic changes in the skin. The hypersensitiveness to cold, as expressed by the tendency to attacks of pallor and cyanosis, the frequent improvement of the patients when transported to warmer climates, the spontaneous improvement which may occur following some acute febrile reaction, and the temporary improvement which can be obtained by inducing fever by some nonspecific method, give impressive clinical confirmation of the fact that the vasomotor element is significant. The appearance and behavior of the capillaries of the skin demonstrate the pathologic hypertonus of the arterioles. Lowering of the temperature of the room by 2 to 3° will induce complete closure of the arteri-

oles, and cessation of the flow of blood in the capillaries. These studies impress the observer with the fact that the available circulation is tremendously impaired by this excessive tendency to spasm. Similar evidence is afforded by the fairly high vasomotor indexes.

Surgical measures applied to the sympathetic apparatus, that now are available<sup>1,5</sup>, permanently interrupt the vasomotor pathways to the vessels of the hands and feet. The fact that cases of Raynaud's disease, selected cases of thrombo-angitis obliterans, and cases of other disturbances associated with vasospastic disorders respond most satisfactorily, is ample basis for utilizing the operative measures in the cases of scleroderma in which the vasomotor element seems to be the primary, and perhaps the major, disturbance.

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# Surgical Treatment of Vasospastic Types of Scleroderma by Resection of Sympathetic Ganglia and Trunks\*

ALFRED W. ADSON, M. D., *Section on Neurologic Surgery,*  
PAUL A. O'LEARY, M. D., *Section on Dermatology and Syphilology,*  
*and*  
GEORGE E. BROWN, M. D., *Division of Medicine,*  
THE MAYO CLINIC, *Rochester, Minnesota*

THE permanent vasodilator effect following resection of sympathetic ganglia and trunks, with its subsequent physiologic changes, has stimulated us to find numerous clinical applications of the procedure. Naturally any disease that arises either directly or indirectly from impaired circulation must be considered. The results obtained by interrupting the vasoconstrictor fibers of the peripheral arteries are determined by the dilatation of the arteries and arterioles affected by the operative procedure. Therefore, it is extremely important to select patients who have nonocclusive lesions of the arteries, and who have vasomotor spasm of the arteries which has resulted in impairment of the circulation. Little, if anything, is to be accomplished by performing resection of sympathetic ganglia and trunks in cases in which there are destructive

changes in the walls of the arteries, such as are found in arteriosclerosis, since these vessels are incapable of dilatation even though the vasoconstrictor fibers are cut. Furthermore, nothing is to be accomplished by the operative procedure if the disease has progressed to such an extent that the arteries have become obliterated by late fibrous changes.

Raynaud's disease is the classical disorder which results from vasospasm, and is the one that has responded most favorably to interruption of the vasoconstrictor fibers. Thrombo-angitis obliterans also falls into this category of vasospastic diseases, inasmuch as the collateral arteries are the site of marked vasomotor spasm, even though there is an occlusive lesion of the principal arteries and veins. The result of the operative procedure, in thrombo-angitis obliterans, is dependent on the degree of spasm of the collateral vessels, the greater the spasm, the greater its release by the operation, with concurrent improvement of the circula-

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tion In turn this means relief of pain, reduction in edema, healing of ulcers, and restoration of function to the extremity

In view of the results obtained in the treatment of Raynaud's disease and thrombo-angitis obliterans, it was apparent that resection of sympathetic ganglia and trunks might be applied to a type of scleroderma involving the skin over the fingers, hands, forearms, toes, feet, and legs, as well as that covering the face, neck, and upper part of the thorax This type of scleroderma apparently develops as a result of vascular disturbance in persons who have complained of cold, wet, clammy hands and feet In a few instances, the cutaneous changes came on suddenly, but more often they were preceded for many years by what may be called mild Raynaud's disease In attempting to explain the sclerotic changes that develop in scleroderma, it is found that the vasomotor spasm is of milder degree than that in Raynaud's disease, but that it is more continuous Therefore the periods of thorough relaxation of the arteries in Raynaud's disease are probably sufficient to bring about restitution of the injury that has taken place during the stage of asphyxia Hence the changes of scleroderma are not seen in true Raynaud's disease The ulceration that takes place in Raynaud's disease probably is the result of sudden, severe constriction of terminal arteries, which do not relax sufficiently during the phase of dilatation to bring about recovery

Curiously, the sclerodermatous changes were more pronounced in the skin of the hands, neck and face than

they were in the skin of the feet. This was probably due to the fact that the existing vasomotor spasm was aggravated by exposure to environmental changes, therefore, one would expect the disease to be more advanced in the uncovered parts of the body, such as the hands, than in the protected parts of the body, such as the feet

#### EVALUATION OF OPERATIVE RESULTS

This review includes a group of sixteen patients, in all of whom bilateral resection of cervicothoracic sympathetic ganglia and trunks was performed through the posterior approach In three patients, bilateral resection of lumbar sympathetic ganglia and trunks had been performed in addition to the operation in the cervicothoracic region The scleroderma was of the moderately diffuse type, and affected the skin of the hands, the arms, the face, the neck, the scalp, the anterior portion of the thorax, the feet and the legs

The patients were divided into three groups, classified on the basis of the relationship of vasospastic phenomena to the development of the disease group 1, primary scleroderma, vasomotor disturbance appearing late in the disease, table 1; group 2, simultaneous development of scleroderma and vasomotor disturbance, table 2, and group 3, vasomotor disturbance preceding the development of scleroderma, table 3

*Group 1, cases 1, 2, and 3*—Definite changes were noted following operation. The symptoms of vasomotor reflex disappeared, the skin became warm and softer or more flexible,

TABLE I EFFECTS OF RESECTION OF CERVICOTHORACIC GANGLIA AND TRUNKS ON SURFACE TEMPERATURE AND ELIMINATION OF HEAT IN HANDS

Case	Surface temperature of fingers* degrees centigrade				Elimination of heat in hands**		Time after operation when records were made, days	
	Before Operation		After operation		Before operation	After operation		
	Right	Left	Right	Left				
1	24.8	25.6	28.7	29.1	15	76	Right side,	52
							Left side,	19
2	25.0	25.3	33.6	33.5			12	
3	27.1	24.6	29.4	28.8	70	140	Left side,	62
							Right side,	35
4	24.4	26.0	32.1	32.2	21	33	9	
5	24.7	24.7	32.5	32.9	45	70	19	
6	25.6		29.1		27	80	28	
9	23.8	22.8	28.1	29.0			40	
10	21.7	19.6	27.8	28.5			16	
11	24.5	24.5	31.1	27.7	18	78	35	
12	27.2	26.7	31.6	30.8	32	47	13	
15	26.6	27.9	31.7	31.9	45	72	71	
16	29.8	28.8	30.7	29.5			35	
Mean values	25.4	25.1	30.5	30.3	34	74		

\*Average of fingers of both hands

\*\*Small calories of heat eliminated for entire hand and number for unit area

pigmentation diminished, mobility of the joints increased, muscular function developed, trophic ulcers healed, and growth of the hair and nails took on new activity. Postoperative study of this group has been limited for the most part to convalescence in hospital, which has not given sufficient time to make final estimations, but it is doubtful if the ultimate results in this advanced group will compare favorably

with the gratifying results obtained in group 3.

*Group 2, cases 4, 5, 6, and 7*—The symptoms, in this group, progressed more rapidly than those in group 3, and were somewhat similar to those in group 1. There was marked fibrosis which was not altered greatly by sectioning of the vasoconstrictor fibers. Postoperative changes in this group were similar to those in group 1. Suffi-

TABLE 2 EFFECT OF INDUCED FEVER AND OF OPERATION ON SURFACE TEMPERATURE.

Temperature in degrees centigrade						
Case	Hands, with normal body temperature	Induced rise in body temperature	Hands, after fever had been induced	Hands, rise due to vasomotor effects	Hands, rise due to operation	Vasomotor index before operation
1	27.1	2.5	36.6	7.0	3.7	2.7
2	23.5	1.6	36.8	11.7	9.2	7.3
3	24.1	1.9	36.0	11.9	8.8	7.3
4	23.0	1.6	37.6	13.0	8.5	8.1
5	28.9	1.7	37.4	6.8	7.6	4.0
6	25.7	1.6	38.0	10.7	4.9	6.6
9	22.8	2.0	34.7	9.9	5.1	6.0
10	21.7	0.8	33.6	11.1	7.8	13.8
11	28.6	2.7	38.7	7.4	5.0	2.7
12	26.4	1.6	34.6	6.6	4.1	6.6
13	27.8	1.2	36.8	7.8		6.5
14	25.9	1.6	37.8	10.3		6.4
Mean values	25.5	1.7	35.6	9.5	6.5	6.5

cient time has not elapsed to give final evaluation of the operative results

Group 3, cases 8 to 16—In the nine cases of this series, the disease had been present for from five to twenty-two years. All patients underwent resection of cervicothoracic sympathetic ganglia and trunks and, in cases 9, 11, and 13, bilateral resection of lumbar sympathetic ganglia and trunks also was performed. In case 9, the resection in the lumbar region was performed twenty-six months before that in the cervicothoracic region. The most impressive improvement was noted in the feet after this lapse of time. The scleroderma had disap-

peared entirely. The feet were warm and dry, and the patient stated that so far as she knew, they were perfectly normal. The only untoward effect of the operation was the extreme dryness in the feet and the tendency to abrasions of the skin over the malleoli from friction of the shoes. For the group as a whole, the percentage of improvement of the condition of the upper extremities varied from 30 to 60 per cent within the period of post-operative observation. The improvement in the condition of the feet in the other two cases in which the lumbar operation had been carried out was greater than that obtained in the hands,



TABLE 3 RESULTS OF OPERATION IN RELATION TO TYPE AND DURATION OF SCLERODERMA

Case	Age, years, and sex	Duration of disease, years	Percentage im- provement with resection of cervicothoracic ganglia and trunks*	Type of sclero- derma in relation to vasomotor disturbance
1	37 M	125	5-10	Primary scleroderma with late vasomotor disturbances
2	41 M	15	10-15	Primary scleroderma with late vasomotor disturbances
3	30 M	2	10	Primary scleroderma with late vasomotor disturbances
4	50 F	15	10-15	Vasomotor disturbances and sclero- derma developing simultaneously
5	55 F	2	20	Vasomotor disturbances and sclero- derma developing simultaneously
6	19 F	2	30+	Vasomotor disturbances and sclero- derma developing simultaneously
7	34 M	35	30	Vasomotor disturbances and sclero- derma developing simultaneously
8	24 M	5	30-40	Vasomotor disturbances preceding development of scleroderma
9	32 F	5	50	Vasomotor disturbances preceding development of scleroderma
10	36 F	5	60	Vasomotor disturbances preceding development of scleroderma
11	34 M	8	30	Vasomotor disturbances preceding development of scleroderma
12	35 F	11	50	Probably a vasomotor form, slowly progressive scleroderma
13	37 F	13	40	Vasomotor disturbances preceding development of scleroderma
14	44 F	15	35	Vasomotor disturbances preceding development of scleroderma
15	57 F	17	40	Vasomotor disturbances preceding development of scleroderma
16	25 F	22	30	Vasomotor disturbances preceding development of scleroderma

\*The results of resection of cervicothoracic ganglia and trunks were estimated at periods of two weeks to five months after operation, and the opinion given was based on the statements of each patient and of at least two physicians. Similar methods were used in estimating the benefits of resection of lumbar ganglia and trunks in the three cases (9, 11 and 13) in which it was done, except that in case 9 the estimation was not made until twenty-six months after operation. In case 9, the percentage of improvement was estimated as 90, in case 11, 80, and in case 13, 80 to 90.

although complete involution of the sclerodermal process, such as that in case 9, was not noted. However, we are of the opinion that, as time elapses, further improvement will take place. In those patients who were observed for longer periods of time after operation, regression of the cutaneous thickening was continuing. Thermometric studies in this group were carried out in six cases. The average surface temperature of the fingers of the right hand was  $25.3^{\circ}\text{C}$ , following operation it was  $30.9^{\circ}\text{C}$ , the mean increase for the group was  $5.6^{\circ}\text{C}$ . For the fingers of the left hand, the mean value for the surface temperature before operation was  $25.2^{\circ}\text{C}$ , after operation it was  $31.3^{\circ}\text{C}$ . The rate of loss of heat in the hands before operation, in three cases, was 32 small calories, and after operation, 66 small calories for each minute.

The improvement in the cases of group 3 was fairly decisive from the standpoints of clinical observation, patients' statements, subjective improvement, and studies of temperature (Figs 1 to 4). Improvement in the cases with fairly long periods of observation was progressive and continuous. Further information on the improvement in this group is afforded by the fact that the number of patent capillaries for each unit area of skin was increased. The capillary flow was accelerated, the blood was of a normal reddish color, and hypertonic disturbances of the arterioles were greatly lessened or had disappeared.

Considering the improvement in the group as a whole, this study of a comparatively small series of cases indicates fairly conclusively that the dura-

tion of the disease and the early vasomotor disturbances are important in the predicting of results from this operation. The high degree of improvement of the condition of the feet, in these cases, is probably due to two factors: (1) the effect on vasodilatation of resection of the ganglia and trunks is more complete in the feet than it is in the upper extremities, and (2) when the disease is present to a marked degree in the upper extremities, the condition in the feet is less advanced, the organic changes are not advanced. Involution and possibilities of cure would be anticipated on this basis.

#### OPERATIVE TECHNIC

Leriche, in attempting to treat scleroderma by interrupting the vasoconstrictor fibers, first performed periarterial sympathectomy, on the basis that the innervation of the artery was centrifugal in origin. Later it was his impression that there probably existed a centripetal innervation, this, also was disproved, he then held that there probably existed an intramural sympathetic ganglion, the removal of which would produce relaxation of the artery below the site of operation. However, the work of Kramer and Todd, and Potts has proved rather conclusively that the vasoconstrictor innervation is distributed to the artery at various levels corresponding to the cutaneous and somatic segments. Hence, if it were hoped to accomplish relaxation of vessels, it would be necessary to interrupt the sympathetic vasoconstrictor fibers at some point above their entrance into the spinal nerves. This clearly indicated ramsection, or ganglionectomy and resection of trunks.

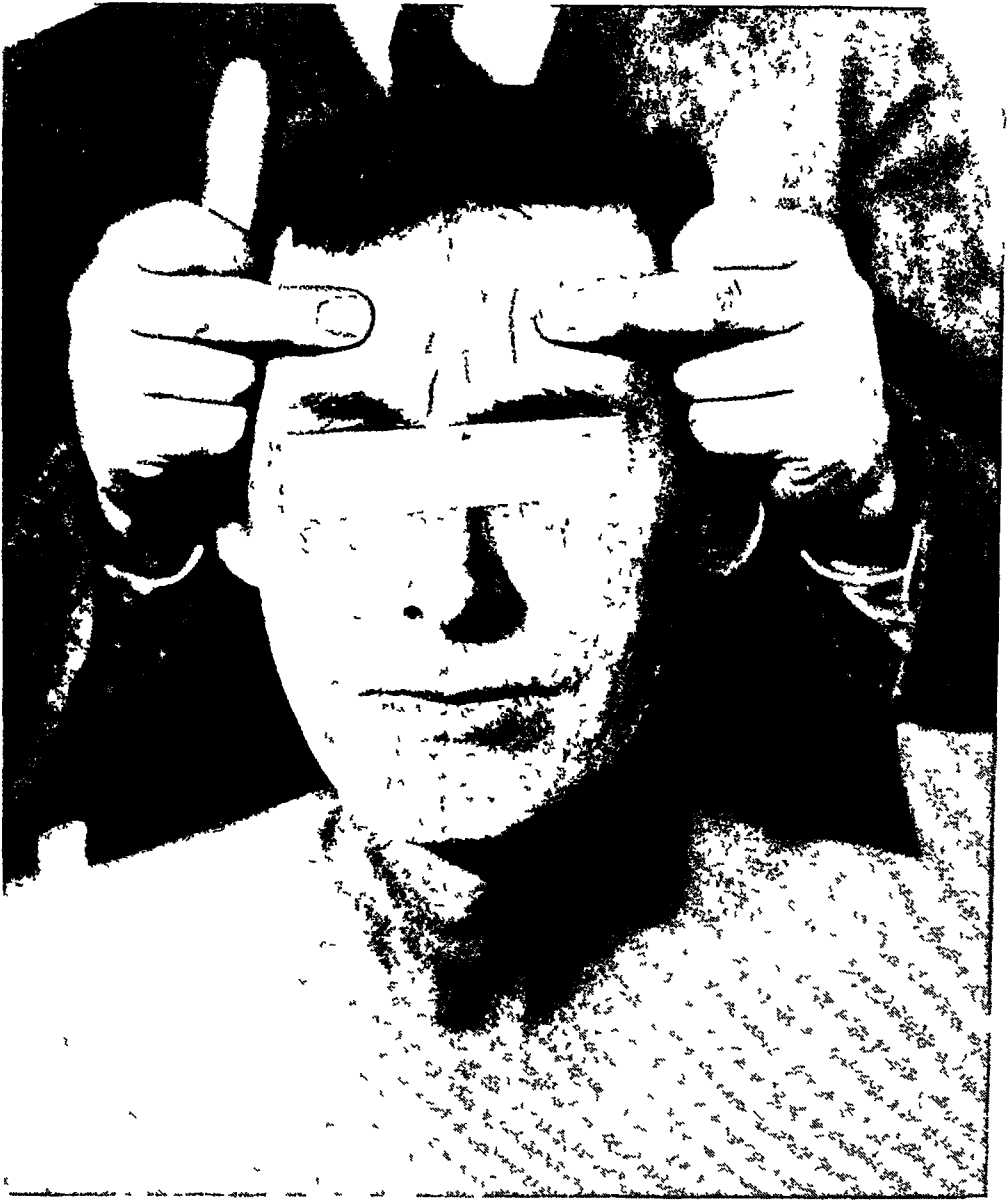


FIG 1 The hide-binding of forehead before operation

Our experiences in the treatment of Raynaud's disease of the lower extremities taught us that if we were to accomplish thorough relaxation of the vessels, it was necessary not only to divide rami, but to resect the lumbar ganglia and the sympathetic trunks, since the distribution of the rami is so irregular that they are easily overlooked. By resecting the lumbar trunks above the second lumbar gang-

lion and below the fourth lumbar ganglion, and removing the intervening ganglia, we were able completely to interrupt all vasoconstrictor fibers going to the arteries of the lower extremities. A similar procedure, therefore, was carried out in the treatment of scleroderma of the feet and legs. We did this October 17, 1927, with excellent results, which consisted in relief of pain, improvement in circula-



FIG 2 The skin of forehead is more easily wrinkled as a result of the softening. Photograph taken fourteen days after operation.

tion, partial restoration of the skin to its normal state, and partial recovery of muscular function. The patient is now free from all complaints due to exposure to cold. She has complained of her feet being too warm during hot weather, but said that they are not warm enough to be troublesome. The skin is dry, because of the interruption of the sympathetic fibers to the sweat

glands, and is rather thin over bony prominences. New vessels have grown into the atrophic regions, as can easily be demonstrated by simple observation and by compressing the skin. The muscles of the leg have again taken on their normal size and present the fusiform appearance of normal muscle. The function of the lower extremities has been completely restored.

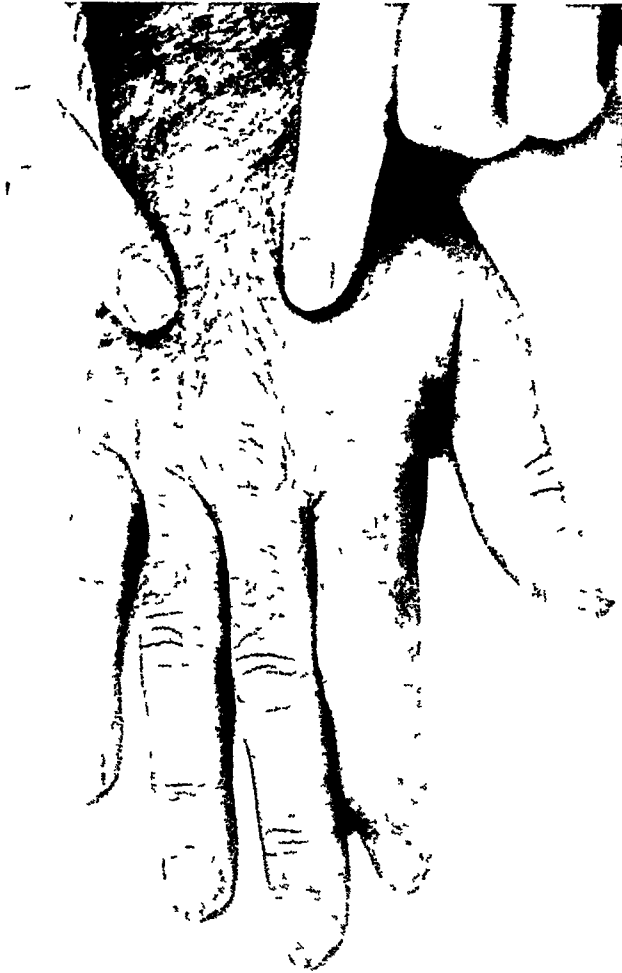


FIG 3 The induration of skin is demonstrated by the difficulty in wrinkling

At the time of her first operation, the patient had a more aggravated form of sclerodactylia of the upper extremities with involvement of the skin and muscles of the upper extremities, face, and neck. However, inasmuch as we had not perfected an operative procedure for thoroughly interrupting the vasoconstrictor fibers, which supply this region, the patient was compelled to return home. Since then she has returned to us and on October 29, 1929, submitted to the newer procedure of resection of cervicothoracic sympathetic ganglia and

trunks, through the posterior intrathoracic approach.

This patient gave us an excellent opportunity to study the results of operation on the lower extremities in comparison with the progress of the disease in the upper extremities, which had not had the benefit of operation. It became obvious that, unless something is done to relieve the vasomotor spasm, which apparently is the underlying factor in the production of this particular type of scleroderma and myositis with atrophy, the disease will progress, producing fibrosis of the

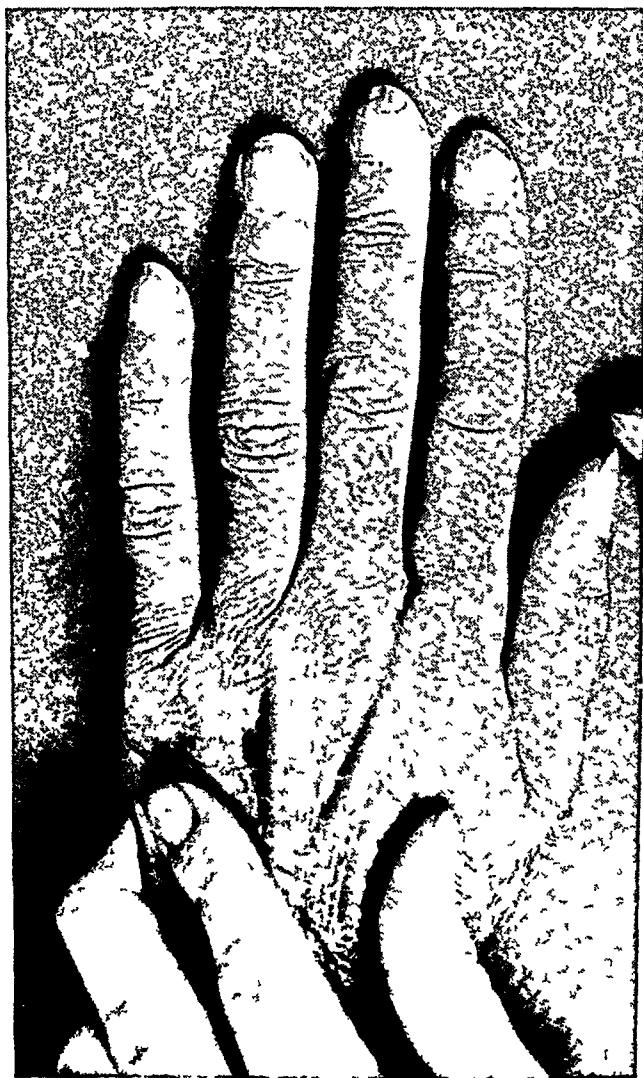


FIG 4 The skin is now readily picked up by fingers of one hand

skin, subcutaneous tissue, ligaments, fascia, and muscles. Finally ulceration takes place over the bony prominences and complete invalidism ensues.

This same patient, following resection of cervicothoracic sympathetic ganglia and trunks, began immediately to improve. The skin became warm, giving evidence of arterial relaxation and increased blood supply to the skin over the fingers, hands, arms, thorax and face. Relaxation of the skin was taking place at the time of the patient's dismissal, and strength was returning to the muscles of the hands,

forearms, arms, and the masseter muscles. Relaxation of the masseter muscles was taking place, and the patient was able to open her mouth wider than before the operation. Relaxation of the muscles of the tongue likewise was taking place, so that she was able to extrude the tongue farther than before the operation. On the whole, it appeared that recovery would take place in the skin and the adjacent tissues of the upper extremities similar to that which had taken place in those of the lower extremities.

Bruning reported success in the treatment of Raynaud's disease and

scleroderma of the upper extremities by resection of the stellate ganglion through the anterior superior approach. Although it is possible to get such a result occasionally by the procedure described by Jounnesco, it is usually met with failure. Kuntz has shown that removal of the so-called stellate ganglion, by the anterior approach, does not interrupt all of the sympathetic vasoconstrictor fibers to the arteries of the hands. Therefore, a surgical procedure was proposed and carried out, which consisted in a posterior intrathoracic approach, which would permit resection of the thoracic trunk, below the second thoracic ganglion, with complete removal of the lower cervical and first and second thoracic sympathetic ganglia, with the intervening trunk. This was done by resecting the proximal portion of the second rib, with the transverse process of the second thoracic vertebra and thus opening the thoracic cavity on each side of the spinal column. But again difficulty was encountered, because occasionally the lower cervical ganglion was a circumscribed structure, separated from the first thoracic ganglion, but communicating with it through the sympathetic trunk. In such cases the lower cervical ganglion could not be delivered into the wound and could not be satisfactorily resected. The result was that the Horner's syndromes were unequal, and that occasionally areas which perspired still existed on the hands. This suggested, of course, that some sympathetic vasoconstrictor fibers had entered the upper portion of the lower cervical ganglion the lower part of which had been resected. The remain-

ing upper portion, in turn, had sent fibers on to the ciliary ganglia and to a localized area on the skin over the hand. The procedure was then changed and the thorax was entered through an opening made by resection of the first rib instead of the second, thus permitting exposure of the first sympathetic thoracic ganglion between the eighth cervical and the first thoracic nerves. Then it was possible to bring into the wound, with ease, and to resect the lower cervical, the first thoracic, and occasionally the second thoracic ganglia, with the intervening trunks. In case the second thoracic ganglion was low-lying the first thoracic nerve was thoroughly dissected free from all communicating ramus and fibers, from the intervertebral foramen to its juncture with the eighth cervical nerve to make up the lower trunk of the brachial plexus. Thus, all white ramus, as well as all gray ramus extending upward from the two upper thoracic ganglia and nerves, and the trunk which carries ramus to the upper cervical ganglion were interrupted. This procedure, which we have carried out many times in these varied peripheral vascular diseases, has given evidence of interrupting completely all sympathetic fibers above the second thoracic nerve, with the result that the Horner's syndrome is always bilateral and complete on both sides, and that no areas of perspiration remain on the skin of the face, neck, arms, or hands.

#### LIMITATION OF SURGICAL TREATMENT

In the late stage of the disease there is marked increase of the collagen in the corium, which interferes with the

flow of blood in the superficial vessels. Because the blood vessels with the lowest pressure, such as the venules and capillaries, are compressed, they become distorted, and obstruction of the blood supply is produced. In addition to this compression, there is definite evidence of obliterative disease in the arterioles and consequent thrombosis of the vessels. As a result of these two processes, there is atrophy of the appendages of the skin besides trophic ulcers and destruction of the finger tips. It is evident that these changes will not undergo involution by medical or surgical treatment, accordingly, in the selection of cases for operation, it is important that surgical treatment should be carried out as early in the disease as possible. It appears to us most unlikely that vasodilatation, if produced in the late or advanced stage of the disease, will produce impressive degrees of improvement. In spite of these deductions, surgical treatment may be justified in advanced cases because of the symptomatic relief obtainable, and because of the inadequacy of any other type of treatment.

We feel it essential to discuss the problem frankly with the patient, so that he will clearly understand the probable degree of improvement to be obtained. In view of the fact that the ultimate prognosis in the majority of these cases is extremely grave, that the condition is usually progressive, and that deformities develop, one is justified in stating clearly to these patients that the smallest amount of improvement is worth having. When arthritis and flexion deformities are present improvement will not be complete, and

physiotherapeutic treatment should follow surgical measures. It is not possible to predict the effects on the skin from increasing the circulation, for this depends on the amount of vascular occlusion present, and only careful study of the changes after operation in cases representing different forms of the disease would answer this question.

#### POSTOPERATIVE SEQUELAE

The increased temperature of the skin which follows the operation is a prominent manifestation, but is not troublesome, the patient may sleep with the extremities uncovered. He may complain, during the hot weather, of itching. This is probably due to the dryness of the skin which is a result of the operation, since the fibers to the sweat glands run with the vasoconstrictors and must perforce be divided with the vasomotor nerves. The dryness and itching are readily relieved by oiling the skin with lanolin or coconut oil. The vasodilatation does not produce the symptoms of erythromelalgia. The Horner's syndrome must be accepted if complete interruption of vasomotor nerves of the upper extremities is to be effected. A unilateral Horner's syndrome is a disfiguring and annoying phenomenon, but a bilateral one is rarely complained of.

We have encountered difficulty in the healing of the surgical wound in four cases. On removal of the sutures at the time usual for other lesions, the edges pulled apart, and there was little evidence of any healing having taken place. In two cases, we resutured the thoracic wound three times, and finally had to let it granulate from the



muscular layer, which always healed. This trouble is now overcome by using long tension sutures of silkworm-gut which are left in place until healing has taken place.

Following operation in advanced cases, the patients have experienced pain in the large muscles of the included region. This manifests itself in about a week after operation, is severe for two or three weeks, gradually diminishes in severity, and disappears in eight or ten weeks. It apparently is due to the engorging process that takes place in the vessels throughout the muscles, following the vasodilation.

A few patients have complained of localized tenderness, for a short time, along the brachial nerves. At first we suspected this might be due to trauma of the eighth cervical and first thoracic nerves during the operation, but when other patients did not have such pain after operation, we had to look for another explanation, and concluded that it is due to the process of revascularization, since the pain always disappears as recovery takes place. Exhaustion is a pronounced symptom in this group, and the greater the exhaustion before operation, the longer time is required for recovery from it following operation.

#### SUMMARY

It has been our purpose to call attention to a group of patients who

have complained chiefly of scleroderma affecting the skin of the hands, arms, face, neck, feet and legs, and in whom this condition is related to a vascular disturbance manifested by chronic hyperactivity of the sympathetic nerves supplying these regions. At the onset, these patients have complained of cold, clammy, wet, and cyanotic hands and feet, followed by swelling, hyperpigmentation and pain. Subsequently, as a result of the cutaneous sclerosis, there is tightening and hardening of the skin. Weakness and atrophy of the muscles ensue, with deformity and ankylosis of the phalangeal joints. Resection of the sympathetic ganglia and trunks has been advocated and carried out in this group, with the purpose of improving the circulation by relieving the vasomotor spasm, and thus dilating the arteries and arterioles.

The surgical results depend on the vascular relaxation accomplished. Hence it is important to make a careful selection of patients who present vasospastic phenomena. It is unwise to operate in the advanced cases, which fail to respond favorably to the vascular tests. It is obvious that operative procedures should be instituted early in the course of the disease in the phase in which the condition resembles that in Raynaud's disease, in order to check the disease and improve the existing symptoms.

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# The Relation of Endemic Goiter to Mental Deficiency

O P KIMBALL, M D, *Cleveland, Ohio*

and

J CARLTON MARINUS, M D, *Detroit, Michigan*

**E**NDEMIC goiter has occupied a prominent place in medical literature from the time of our earliest medical writings. We also find references to this age old disease in our ancient manuscripts.

We have definite records of cretins since early Roman history, but it was not until the beginning of the 16th century that the Swiss physician, Paracelsus, described cretinism in detail and emphasized the relation of cretinism to endemic goiter. In 1800, appeared Fodere's basic essay on "Goiter and Cretinism", in which he states that "Goiter is the first degree of a degenerative process in which cretinism is the last step." Again we have the French physician, Morel, expressing this same relation in the statement "Goiter is the first step on the road that leads to cretinism." Throughout the last half of the 19th century we have many volumes dealing with endemic goiter, cretinism, deafmutism and certain types of congenital feeble-mindedness, with definite impressions that the primary cause of all of these conditions is the same.

The scientists of Europe early recognized the intimate relation of goiter to mental deterioration and their governments foresaw the tremendous social responsibility of this disease. A com-

mission to study every phase of endemic goiter was appointed by the Sardinian government in 1848, and by the French government in 1864. In 1908 the Swiss government appointed a goiter commission, and in 1915 the Italian government took similar action.

In our mildly endemic districts we were not at first greatly impressed by the possibility that many cases of mental retardation were due to endemic goiter, but with each survey through our school population, it became more evident that a great many children with congenital goiter showed nervous and mental defects which in some cases resembled mild cretinism. In the study of large numbers of goitrous children, one saw every grade of mental deficiency from the slightly subnormal to cretin idiocy. In some cases, the etiology of the mental status seemed obvious, but in the majority it required a careful study of the family history, of the condition of the mother during pregnancy and of the entire life of the child, before an accurate estimate of the relation of the mental deficiency to congenital hypothyroidism could be made. To clarify this relation is the purpose of this study.

In 1924 the Michigan State Department of Health made a survey of all the school children in four counties

The counties were so located as to give a fairly accurate cross section of the goitrous conditions throughout the state. In this survey all boys and girls from the first to twelfth grades were included and a total of over 36,000 were studied. In each of the four counties, the children were divided into the goitrous and non-goitrous, and the data of each county showed that ten per cent more goitrous children than non-goitrous were on the delinquent list. In this survey we did not have mental tests and rating to determine the delinquency, but if a child had been held back one or more grades he was classified as mentally retarded and this same mental retardation was found more frequently among the goitrous than non-goitrous. We now know that many cases of mental deficiency among those classed as non-goitrous were due to a maternal hypothyroidism during the congenital life of the child without affecting the thyroid sufficiently to produce a palpable goiter. Therefore, the thyroid was diagnosed as normal and the child classed as non-goitrous.

In 1925-26 we studied all the children of six counties in Ohio and exactly the same conditions were found as throughout Michigan. During this study of 56,000 children we were greatly impressed by the frequency of the number of cases in whom we had found mental retardation and congenital goiter. The mental rating was not reported in many of the schools, therefore we cannot report definite data from this survey. However, this etiological relation of endemic goiter to subnormal mentality impressed us so strongly that the researches herein re-

ported were undertaken in order to obtain accurate data on this point.

During the summer of 1928 the research committee of the school board of the Detroit public schools decided to make a special study to correlate the physical and mental condition of each child in the subnormal classes. The enrollment of their special schools was more than 4,500 at that time, and increasing faster than they were prepared to care for them. They thoroughly appreciated the fact that the equipment of more special schools for this group was not the final answer. Therefore, a plan was evolved to study each child of this special class, determine the cause of the mental deficiency, and to treat the condition where possible. What was considered most important, however, was to find some method to prevent the conditions responsible for the mental delinquency. It was the opinion of the committee that in many cases some glandular disturbance was responsible for the abnormal mental growth, and to determine the facts on this point each child was studied primarily for endocrine dysfunction. This investigation began in October, 1928, in cooperation with the Departments of Special Education and Psychologic Clinic of the Detroit schools. Most of the routine physical examinations in the clinic were made by Dr. Marinus and the first studies in the school for the detection of endocrine problems were made by myself.

For obvious reasons a thorough examination of the children in the school could not be made. In fact we did not ask or claim to make an examination, but called it only an inspection. For this inspection we had before us a card

giving chronological and mental age, weight, height and his previous health examination by the regular school physician. This showed his rate of growth and any defects of sight or hearing, we also had their findings on chronic infection, teeth, goiter, anemia and posture. Our inspection included size, body proportion, fat distribution, posture and any bony defects, also texture of skin, hair and nails. We examined teeth and thyroid carefully in every case. By this method the cases for further endocrine study at the clinic were selected and this study group averaged twenty per cent of the total number inspected in the school. Our completed study shows that seventeen percent of the children of the special schools suffer some endocrine dysfunction. Whether this dysfunction is the basis of the abnormal mental growth, is the question that this investigation is meant to answer.

Each study case was brought to the clinic by the mother. This is important, for inspection of the parent is most helpful in the final diagnosis. Our study here started with the mother, her condition during pregnancy and history of goiter, then the birth history and early life of the child, the age of teething, walking and talking, early childhood diseases and nutritional disturbances. At this time, a careful examination is made with the child stripped, with measurements of trunk and extremities for body proportions. In the boys development of the genitals is noted.

We assumed that any endocrine disturbance which was sufficient to cause mental retardation would also leave some mark on the child's physical de-

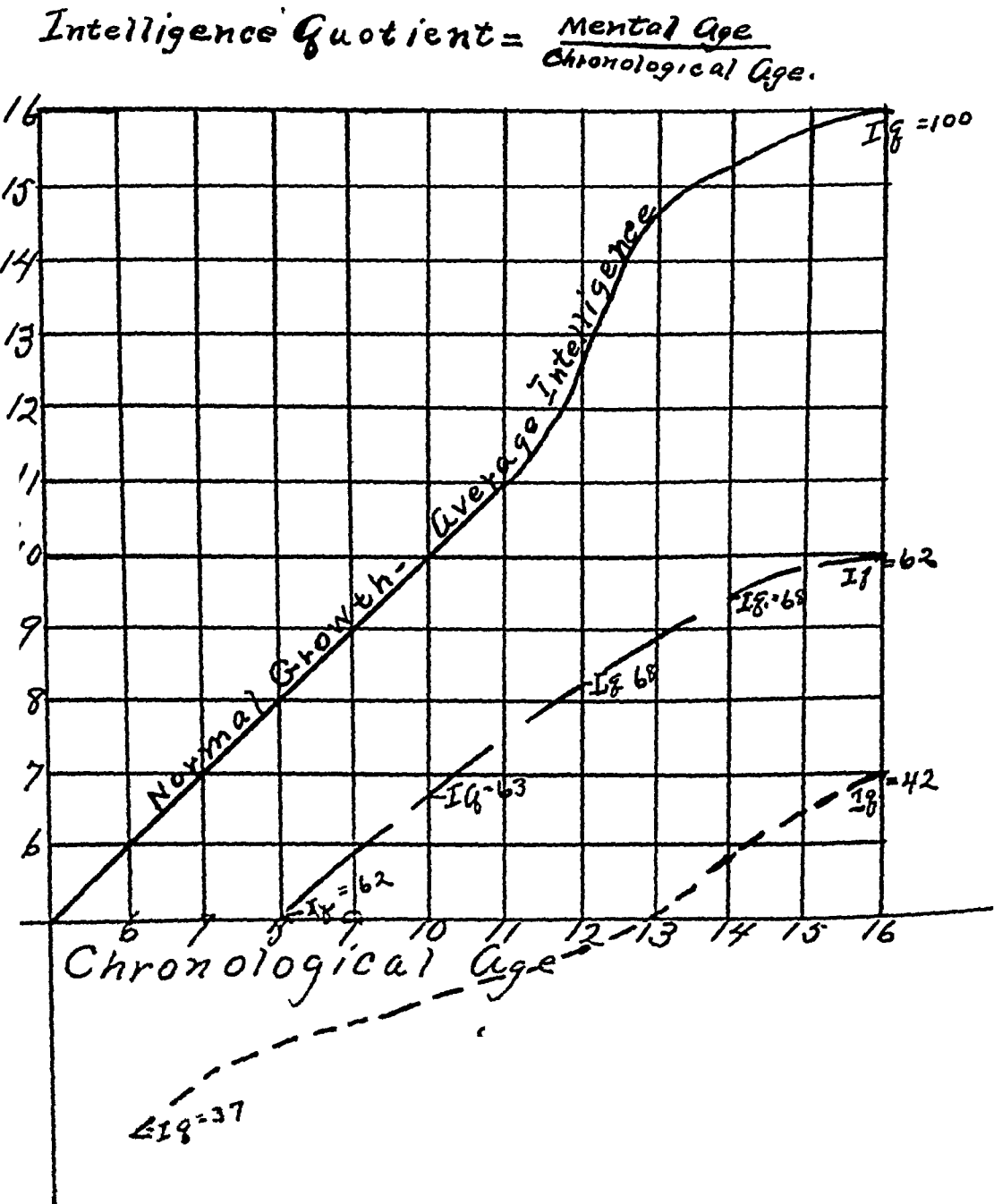
velopment. Therefore, our diagnosis was made from clinical study with the aid of such laboratory tests as basal-metabolism, blood-count, blood-Wassermann and in a few cases x-ray.

This investigation during the past two years includes 3,548 mentally subnormal children. Of this number, 712 showed some endocrine dysfunction, approximately seventeen percent. A similar study through the Detroit schools in 1922 by McGraw showed twenty-four percent with endocrine problems. Of these 712 endocrine problems, 281 are definitely the result of congenital hypothyroidism, or eight percent of all mental defectives of the Detroit schools are due to endemic goiter. If studies from the state institutions were included, ten percent of all the feeble-mindedness would be found to be the result of endemic goiter. In countries where endemic goiter is more severe and the condition has existed throughout generations, as in Switzerland, the number of feeble-minded due to it creates a real social problem. We do not need further proof that the mental status of the 2,000 cretins of the city of Berne is the direct result of endemic goiter, but its responsibility to the 4,500 subnormals of Detroit is not quite so obvious. Yet I am certain that in our mildly endemic districts many of the children classed as subnormals are as definitely related to endemic goiter as our cretins. They are defective because of a maternal hypothyroidism during their congenital life. The severity and duration of the hypothyroidism and the age of the child determines the relative damage.

Of the 281 cases diagnosed as congenital hypothyroidism, 205 have had

repeated intelligence tests so that one can study their mental growth. Ninety, or forty-four percent of these 205, approach the normal rate of growth. They maintain a constant intelligence quotient, but always below normal. A typical example of this group is shown by the graph in Fig. 1. A child of eight years has the mental age of a child of five years or an I.Q. of 62. At sixteen years he still has an I.Q. of 62. The

graph of his mental growth is very similar to the normal average. The lower line in Fig. 1 graphically represents the mental growth of a low mentality. This boy is from the group diagnosed as hereditary feeble-mindedness. This group comprises at least two-thirds of all the feeble-mindedness in every community and is not an endocrine problem. The graph however, demonstrates the tendency to a gradual



increasing intelligence with the usual rise at puberty, even though very sub-normal

The psychologists of our special schools have for several years been studying a group of children whose intelligence quotient keeps falling. In most of these the gradual fall from year to year can mean but one thing, *i.e.*, the mental age has reached its height while the chronological age goes on, and consequently, a decreasing I Q. Among the glandular study cases, we found 117 had shown a persistent decrease in intelligence and further, when our cases had been classified according to diagnosis into thyroid and pituitary groups, we found that ninety-three, or eighty percent of those with falling intelligence were in the congenital goiter group. The other (twenty-four) were in the pituitary, anterior lobe deficiency class. On re-study of the twenty-four cases found in the pituitary group, we were impressed by the possibility of a maternal hypothyroidism being the underlying factor in each of these cases, yet at present the pituitary deficiency predominates.

It is a well established fact that cretins are predestined to a fixed low mental age, beyond which they can not go. If untreated, they seldom go above a mental age of six years. Those recognized in infancy or early childhood and treated adequately, appear to gain rapidly for a few months or a year, then go along at the same mental age, approximately eight years, instead of six as the untreated cretins show. With their mental age fixed, their I Q naturally goes down. There are eight cretins in this study, three of whom have been treated adequately since infancy.

Then mental growth is shown graphically in Fig 2 (broken line). The mental growth of the five untreated cretins is shown in the dotted line of Fig 2. The mental limit of the untreated is just a little under six years, while the three who were given thyroid extract from infancy have been raised to approximately eight years. Their graphs are strikingly similar, reaching their maximum comparatively early, and holding the same mental age thereafter. The usual rise at puberty is not seen.

We have learned nothing new about cretinism. We mention this small group only to re-establish in your mind the type of mental growth that they invariably show, the pre-destined maximal mental age of a child of six or eight, beyond which they cannot rise. Also to state in detail, what Paracelsus pointed out four hundred years ago that this fixed low mentality is the result of a severe maternal hypothyroidism during the second and third months of foetal life. The whole physical development is limited because the vascular system has been irreparably damaged by the stultifying effect of the maternal hypothyroidism, indirectly due to endemic goiter.

Of the 205 cases of congenital hypothyroidism whose repeated mental tests indicate their mental growth, ninety-three or forty-five percent show a falling intelligence quotient or a fixed mental age. The graphic representation of the mental growth of these ninety-three practically duplicates the mental growth of the cretins. Yet, they are not cretins physically, but certainly they have suffered the same lack of develop-

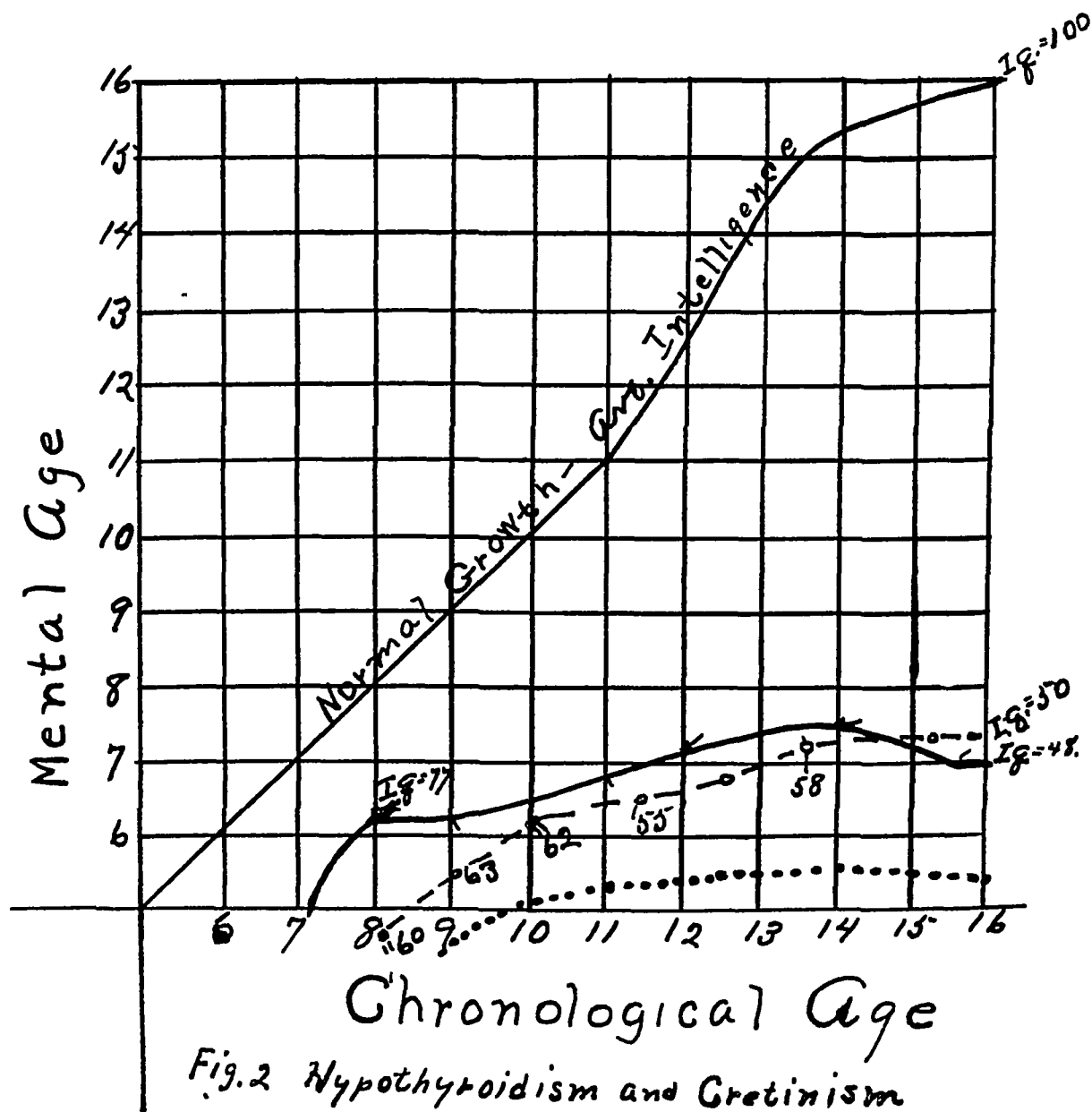


Fig. 2 Hypothyroidism and Cretinism

ment of the cortical areas and the mental growth is thereby limited

The mental growth curves of all of this group are practically identical. The one shown (heavy line, Fig. 2), is of a girl of sixteen with intelligence tests each year since the age of eight. She is typical of this congenital hypothyroidism group since her family history immediately rules out hereditary feeble-mindedness. Her mother gave a clear cut history of marked hypothyroidism during the first half of her pregnancy. The girl has a definite congenital goiter

with a persistent thyreo-glossal stalk. Also, an incomplete development of her first molars. At the age of eight and one-half years her IQ was 77. She showed a slight increase during puberty, but has a decline following this change. At the age of sixteen, her mental age was only seven years and two months, or an IQ of 48. In the discussion of this one girl is concentrated our study of 117 children with a falling intelligence quotient—at least 80 percent of all and most probably 100 percent suffer the same mental



defect and as stated above 45 percent of all cases of congenital hypothyroidism show this same type of mental growth. Studying this group with their cretinoid type of mental growth, we are convinced that the etiology of the mental deficiency is endemic goiter.

Also, of this group of 205, twenty-two or eleven percent show a definite increase in their rate of mental growth. Of these, nine had been diagnosed and given thyroid, since childhood with quite evident results. The others must have developed sufficient thyroid to completely offset any deficiency and thereby bringing out the maximal mental development. From this it would be easy to conclude that all we should do, is to make the diagnosis early and give sufficient thyroid. But, we also saw nine who had been accurately diagnosed in early childhood and given thyroid persistently, yet their IQ had gradually decreased. Apparently their mental growth was limited, as the growth curve is the same as the majority of the ninety-three with falling IQ (Fig 2, heavy line). Therefore, it must depend on the lack of development of the cortical areas, or a limitation set on the functional growth of these areas by an abnormal vascular system.

Above, we referred to the development of the teeth as a diagnostic point in the study of congenital hypothyroidism. We have observed many cases where the first permanent molars show an unusual lack of development. Not a condition of decay or irregular formation due to an early gingival irritation, but a lack of development, a very severe hypoplasia limited chiefly to the cusps. The significant fact is that the

first permanent molars are the first of this set to calcify, calcification beginning about the twenty-fifth week of congenital life. This was emphasized strongly in the instance of three colored boys, age eleven to thirteen, all of whom showed congenital goiter with persistent thyreo-glossal stalk, cretinoid type of mentality, yet they were physically well developed. The first molars in each case were as above described. The other teeth showed perfect enamel as is usual in colored boys. I was quite elated over this complete picture of what we were attempting to establish as a fact, so made arrangements with the school dentist to make casts, drawings, x-ray pictures and careful dental study of these three cases. My enthusiasm proved my undoing, for two of the boys could never be found and the third had gone straightway to his dentist and had his peculiar teeth extracted. We were even unable to locate the dentist and therefore have no models to demonstrate this finding. Cretins of course, have notoriously irregular and defective teeth, but these were not cretins and frequently all other teeth were perfect. We feel that the same maternal hypothyroidism that caused the defect in his thyroid gland, could also produce this stultifying effect on his molars, the points of calcification of which, are, just being laid down at the same time that his fetal thyroid is being so disturbed. And further, this same metabolic disturbance effects the neural development then in progress, and most probably the whole vascular system. We offer this observation knowing we have not yet proven the point.

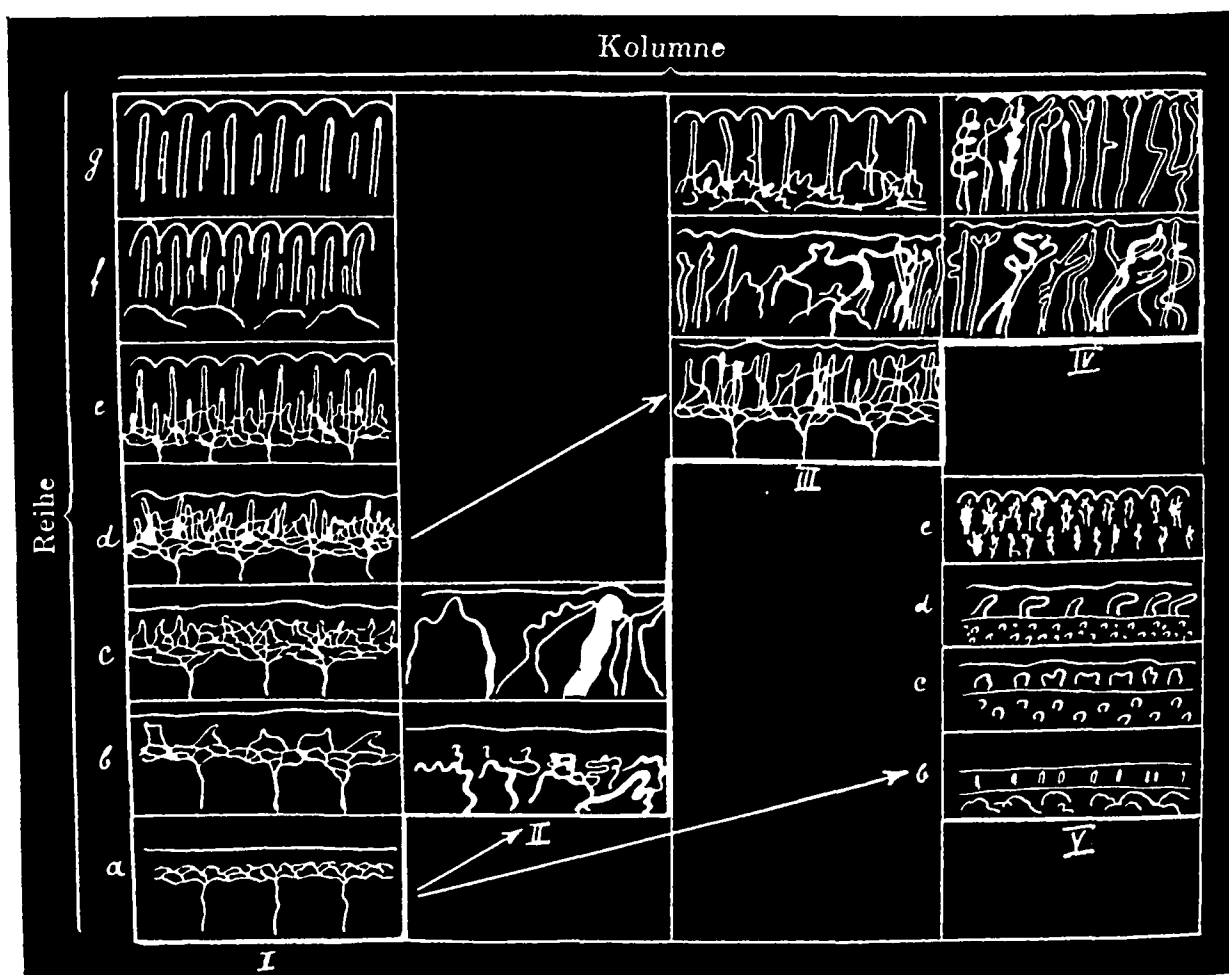


FIG 3 Development of capillaries of the nail bed in normal children, and in hypothyroid cases

For the past five years intensive studies have been made of the abnormal development of the circulatory system in cretinism and its allied conditions. The development of the capillaries of the nail bed have been studied and the pattern of development here is considered our closest index to capillary development elsewhere, especially the brain. The structural picture of the capillaries of the nail grooves according to W. Jaensch and W. Wittneber, was placed in a morphogenetic scheme in 1925 by von Hopfner and expanded by him in 1927. This is shown in Fig 3. Column 1 shows the development in the normal child from birth to one year, by which time the pattern is complete. Column 2 pictures the lack of development which is always seen in

cretins. Columns 3 and 4 show abnormal forms seen in severe hypothyroidism and many cases neuroses and psychopaths due to congenital hypothyroidism. Column 5 are the irregular forms seen most frequently where endemic goiter and cretinism have been more severe. Dr H. Eggenberger of Hirsau, Switzerland, demonstrates this group in his studies.

These authors have been so impressed by the set picture of capillary development in cretinism and hypothyroidism that they use this as a diagnostic measure for congenital hypothyroidism, where there is no clinical evidence. Last year W. Eisenberg reported his psychological study of 3,100 cases of feeble-mindedness, where this diagnostic measure had been applied to each

He finds that the teachability of each child runs parallel with the development of his capillaries. He concludes that subnormal mental conditions should always be studied with congenital goiter in mind.

Regardless of the type of study or the diagnostic measures used, we have come to the same conclusion. It emphasizes the fact that in our mildly endemic goiter districts where we have comparatively few cretins, ten percent of all feeble-mindedness is due to endemic goiter. Stated concretely, the city of Detroit has been paying annually \$40,000 more to educate those made defective by this disease, than it would cost to educate the same number of children with normal average mentality. Yet, their education is very limited, which only emphasizes the amount of time, energy and money we have been paying, unknowingly, to this insidious disease. Therefore, it is with considerable pride that we review the Prevention of Goiter as it has been carried out in the state of Michigan for the past six years. The incidence of goiter in the Detroit public schools has been reduced from forty-two percent in 1924 to seven percent in 1929. The

seven percent still present are nearly all congenital goiter. This point is further emphasized by the fact that in 3,185 children studied last year in this endocrine study, we found only ten or one-third of one percent with hyperplastic thyroid enlargements, and too, most of these children were at the age of puberty. It is now an established fact that the endemic goiter problem in Detroit and Michigan has been solved.

For fourteen years we have been studying endemic goiter and its various manifestations through our school population and each year we appreciate more fully the profound wisdom in the statement of my teacher and co-worker, David Marine, "In the Prevention of Endemic Goiter, we are doing vastly more than Retaining the Normal Curve of the Neck."

We wish to state here that this entire study was made possible by the foresight and assistance of the Research Committee of the Detroit Board of Education. Also we wish to express our appreciation to the Dept. of Special Education and the Psychological Clinic for their assistance and co-operation.

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# The Pituitary Factor in Arteriosclerosis\* Its Experimental Production in Rabbits

By ROBERT C MOEHLIG, M D and EUGENE A OSIUS, M D , *Detroit, Michigan*

**E**XPERIMENTAL production of arteriosclerosis in rabbits has been accomplished by several workers. Anitschkow and Chalutow<sup>1</sup>, Bailey<sup>2</sup> and others, have used various sorts of diets high in fats or fat-like substances to produce these changes.

Certain facts led us to approach the problem from a new angle. The relationship between the pituitary gland and fat and carbohydrate metabolism suggested that the pituitary secretion might be concerned in arteriosclerosis.

While the exact pathogenesis of arteriosclerosis is somewhat in doubt, nevertheless the cholesterol infiltration of the blood vessels is definitely established.

The importance of the suprarenal cortex in cholesterol metabolism is well recognized. Goldzieher<sup>3</sup> says "The intimate correlation between lipid metabolism, adrenal cortex, and atherosclerosis is striking, although its mechanism is far from being clear. The cholesterol disturbance in atherosclerosis and its relationship to the changes of the adrenals has closed the ring of evidence which seems to prove that adrenal hyperfunction is among the most im-

portant factors in atherosclerosis, which we believe is but one particular manifestation of genuine hypertension."

A correlation between the pituitary and suprarenal glands is, therefore desirable. The pathological changes consisting of hyperplasia of the suprarenal cortex with lipid storage, so frequently found in arteriosclerosis, hypertension and nephritis becomes an important link in the arteriosclerotic chain.

In several previous papers, one of us (R. C. M.)<sup>4</sup> has emphasized the fact that the state of the pituitary gland was reflected or mirrored in the suprarenal cortex. The relationship between the two organs is well established and there are many pathological conditions which illustrate it. Aplastic states of the pituitary have a concomitant aplasia of the suprarenal cortex and conversely hyperplasia of the pituitary results in hyperplasia of the suprarenal cortex.

We were led to use posterior lobe extract by the work of Krogh. He concluded from his experiments that the posterior lobe secretes a substance in low concentration which maintains capillary tone. Its pharmacologic pressor effect on the (mesodermic) blood vessels is well known and was further

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\*This work was carried out with the assistance of the technical staff of Harper Hospital Laboratory.

argument for using this substance in the experiments

Rabbits were divided into four groups as follows

*Control Group* Five normal rabbits on a normal laboratory diet consisting of hay, lettuce, vegetables, etc

*Group A* This group consisted of 5 rabbits who were fed on a normal laboratory diet plus the addition daily of 12 cc of cotton seed oil and 4 gms. of anhydrous lanolin for each rabbit This is the diet used by Shapiro<sup>6</sup> and contains a large amount of cholesterol

*Group B* This group consisted of ten rabbits who were placed on the same high fat diet as Group A and in addition received 1 cc of obstetrical posterior lobe extract (Parke-Davis & Co Commercial Pituitrin)\* injected either subcutaneously or intraperitoneally

*Group C* This group consisting of ten rabbits were placed on a normal laboratory diet the same as the control group and in addition received daily 1 cc of posterior lobe extract injected subcutaneously or intraperitoneally

Blood cholesterol estimations (Sackett's<sup>7</sup> modification of Bloor's method) and the weights of the animals were taken every ten days The lanolin and cotton seed oil were heated and then poured onto the food All animals were kept under the same conditions in the laboratory

Except for a few areas of local irritation the animals tolerated the injections

of the posterior lobe extract very well

The first week we gave the injections twice a day and following this once a day over a period of one hundred days so that the average amount injected was 107 cc of posterior lobe extract

The effect of the posterior lobe extract injections was interesting Shortly after each injection the animal became quiet, the peripheral vessels contracted and frequently urine was voided and there were bowel movements The fur of the animals on the high fat diet as well as those on the high fat diet and posterior lobe injections became and remained more ruffled and shaggy, the appearance of the animal's coats bearing a strong resemblance to that of the guinea pig during acute anaphylactic shock (Fig 1)

From this one may conclude that the high fat diet alone may have some influence upon the fur as already reported by Iscovesco<sup>8</sup> He injected suprarenal cortex lipoids into rabbits and found that it increased the growth of the fur

On the hundredth day we began sacrificing the rabbits, by injecting air into the auricular veins Immediate post-mortem was performed The organs were weighed and fixed in formalin The heart and aorta were removed We shall reserve for a future paper the protocol details and microscopical findings

We submit a composite curve of the cholesterol estimations of each group, Charts 1, 2, 3, 4

Because of their importance in the problem of arteriosclerosis and cholesterol metabolism, as previously empha-

\*The pituitrin used in the experiments was kindly supplied us by the Biological Department of Parke Davis & Co It was conveniently put up for us in specially prepared 30 cc vials

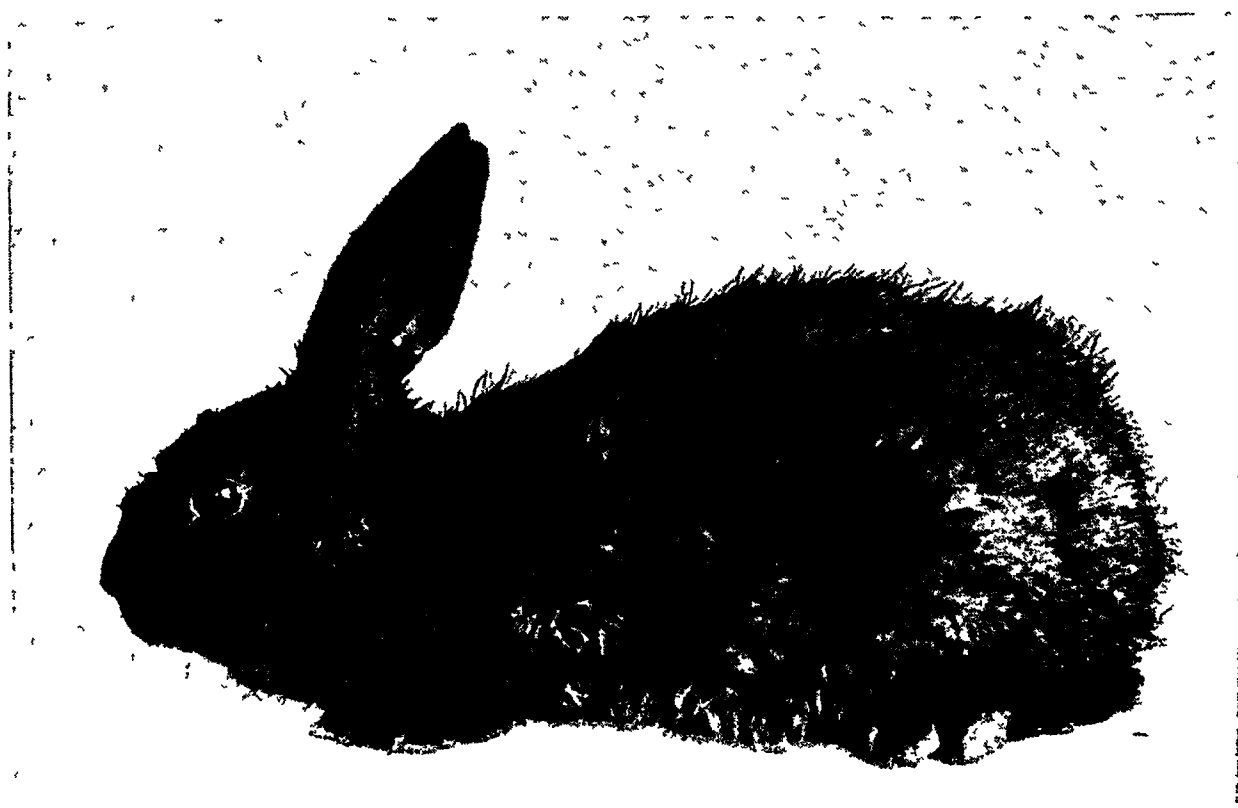


FIG 1 Rabbit on high fat diet showing fur changes

sized, we will give the average weights of the suprarenals

AVERAGE SUPRARENAL WEIGHTS	
Control Group (Normal diet)	278 mgms
Group C (Normal diet plus posterior lobe injections)	415 mgms
Group A (High fat diet only)	435 mgms
Group B (High fat diet plus posterior lobe injections)	639 mgms

The suprarenal weight correlated with the body weight (combined weight of adrenals divided by body weight multiplied by 100,000) gave the following suprarenal indexes

SUPRARENAL WEIGHT— BODY WEIGHT INDEXES	
Control Group	Average index 22.918
Group C (Normal diet plus injections)	" 37.52
Group A (High fat diet)	" 34.52
Group B (High fat diet plus injections)	" 51.75

It is immediately evident when these suprarenal weights are studied that those receiving the posterior lobe injections have a much higher average suprarenal weight than the non-injected groups Likewise this is apparent in the average suprarenal indexes

Under the conditions of the experiment it is apparent that posterior lobe injections increase the size of the suprarenals

Group C, on a normal diet plus the injections of the extract had an average increase over the control of 137 mgms

Group B, on a high fat diet plus the injections of the extract had an average increase of 204 mgms over the group on high fat diet alone and 361 mgms average increase over the controls The increase was much higher than the average weight of the controls The dif-

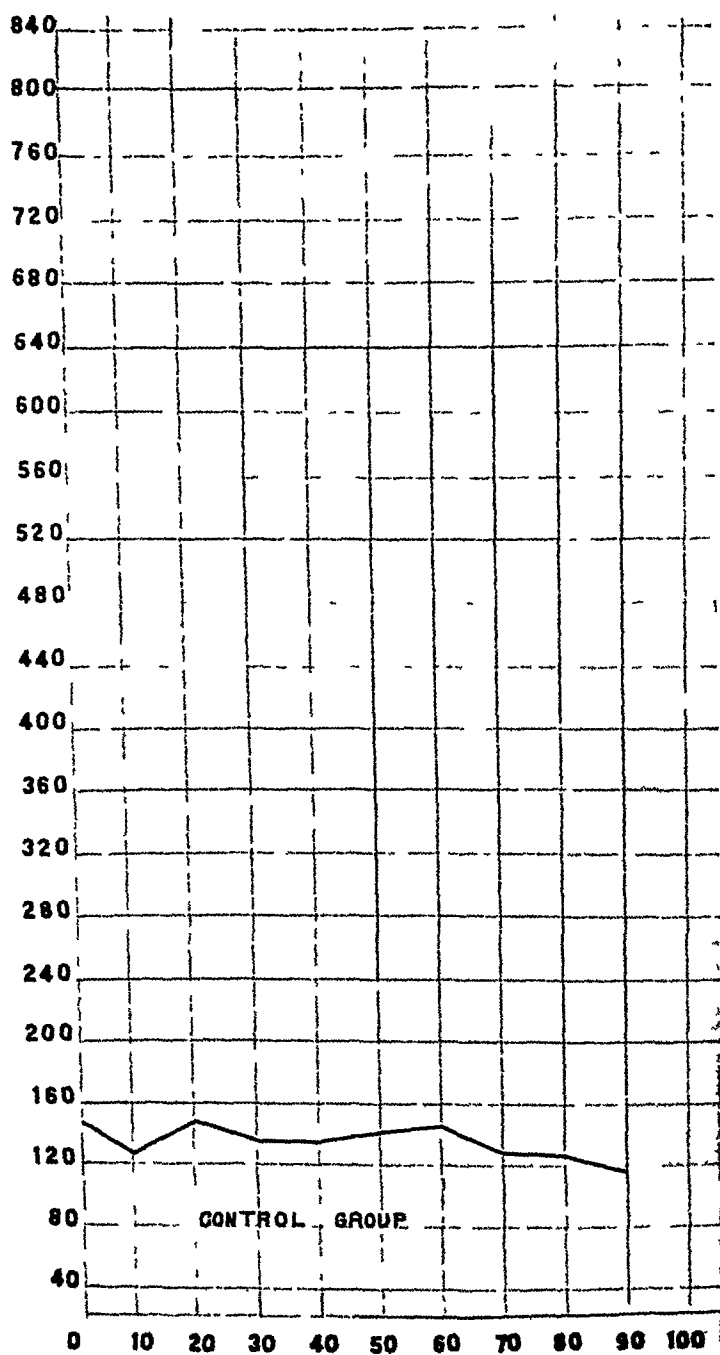


CHART I Horizontal figures represent days Vertical figures represent blood cholesterol in mgms

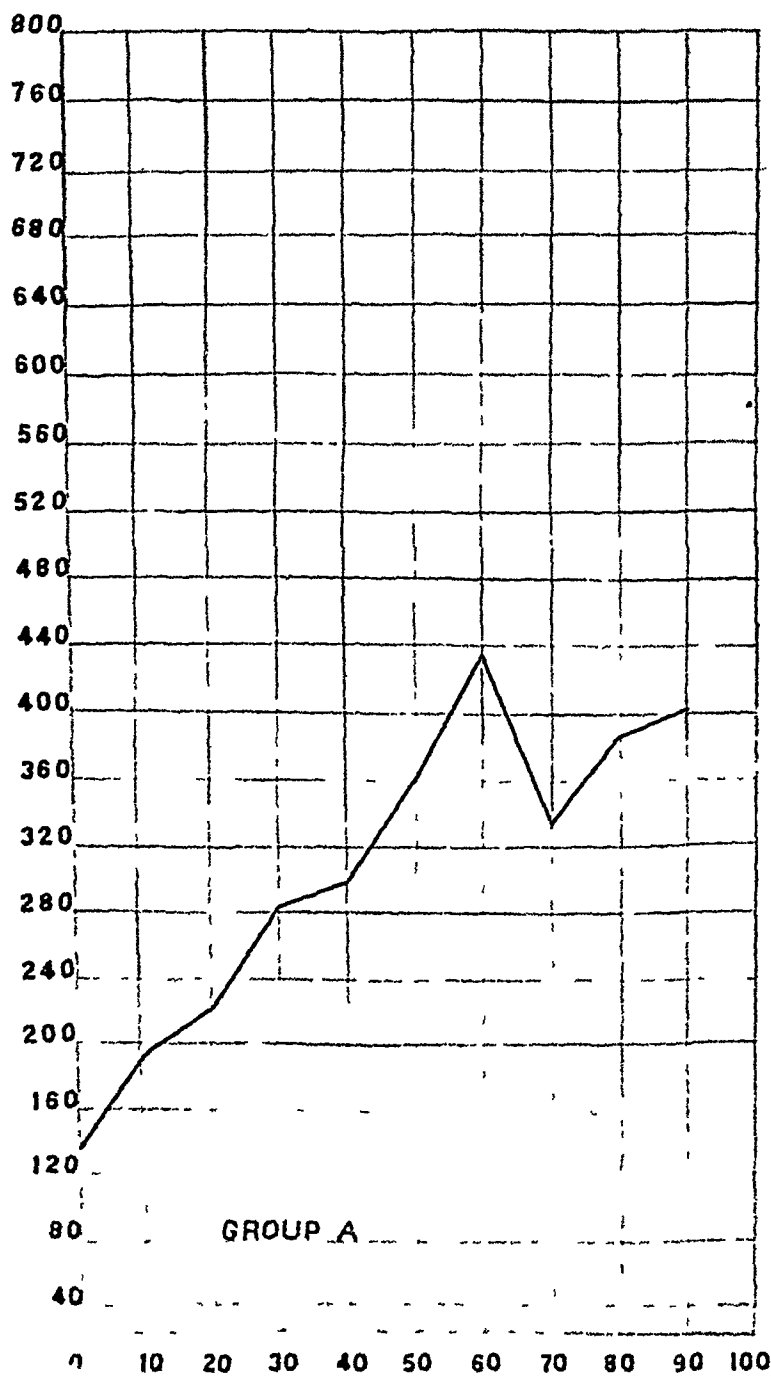
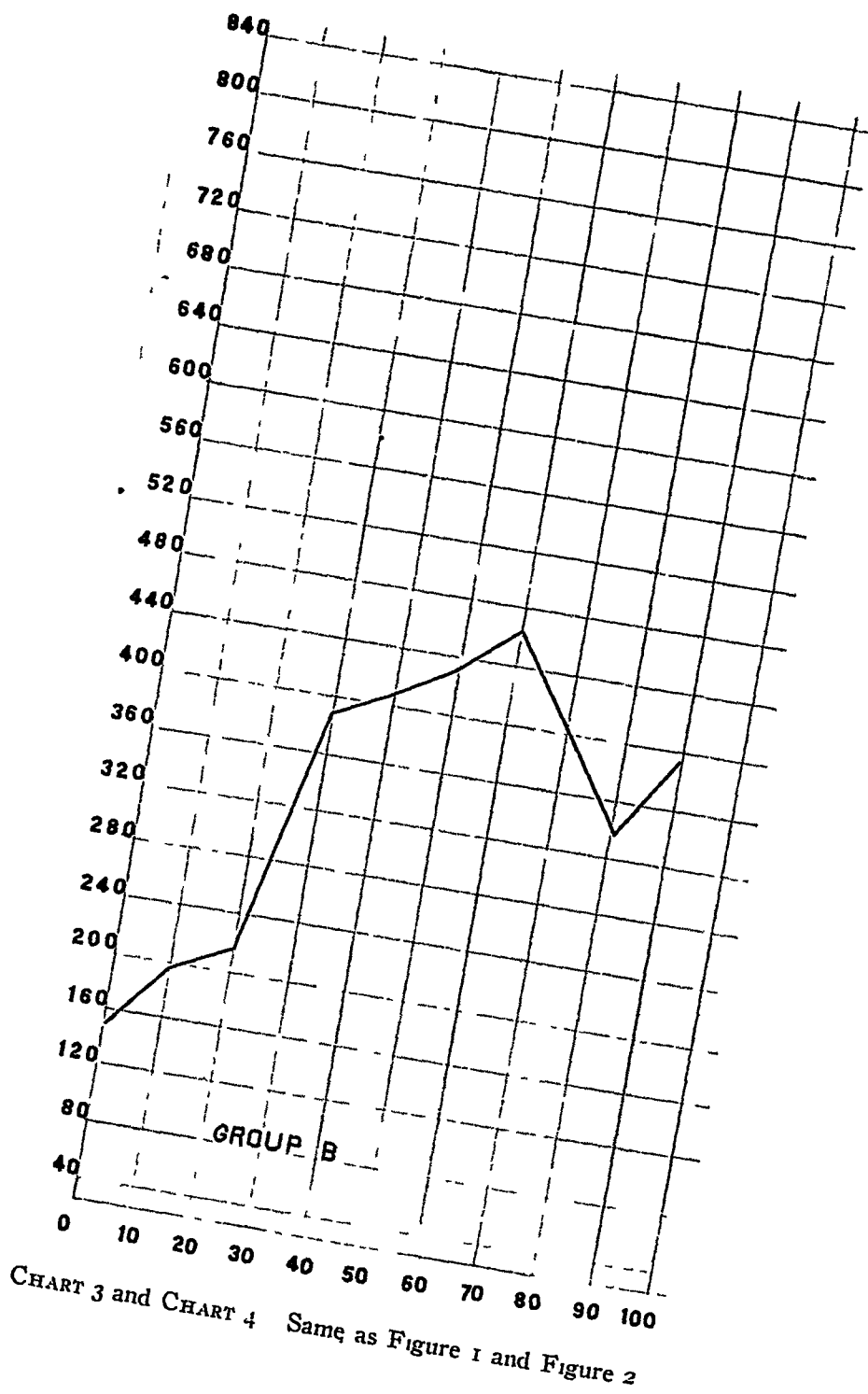


CHART 2 Horizontal figures represent days. Vertical figures represent blood cholesterol in mgms.



# The Pituitary Factor in Arteriosclerosis

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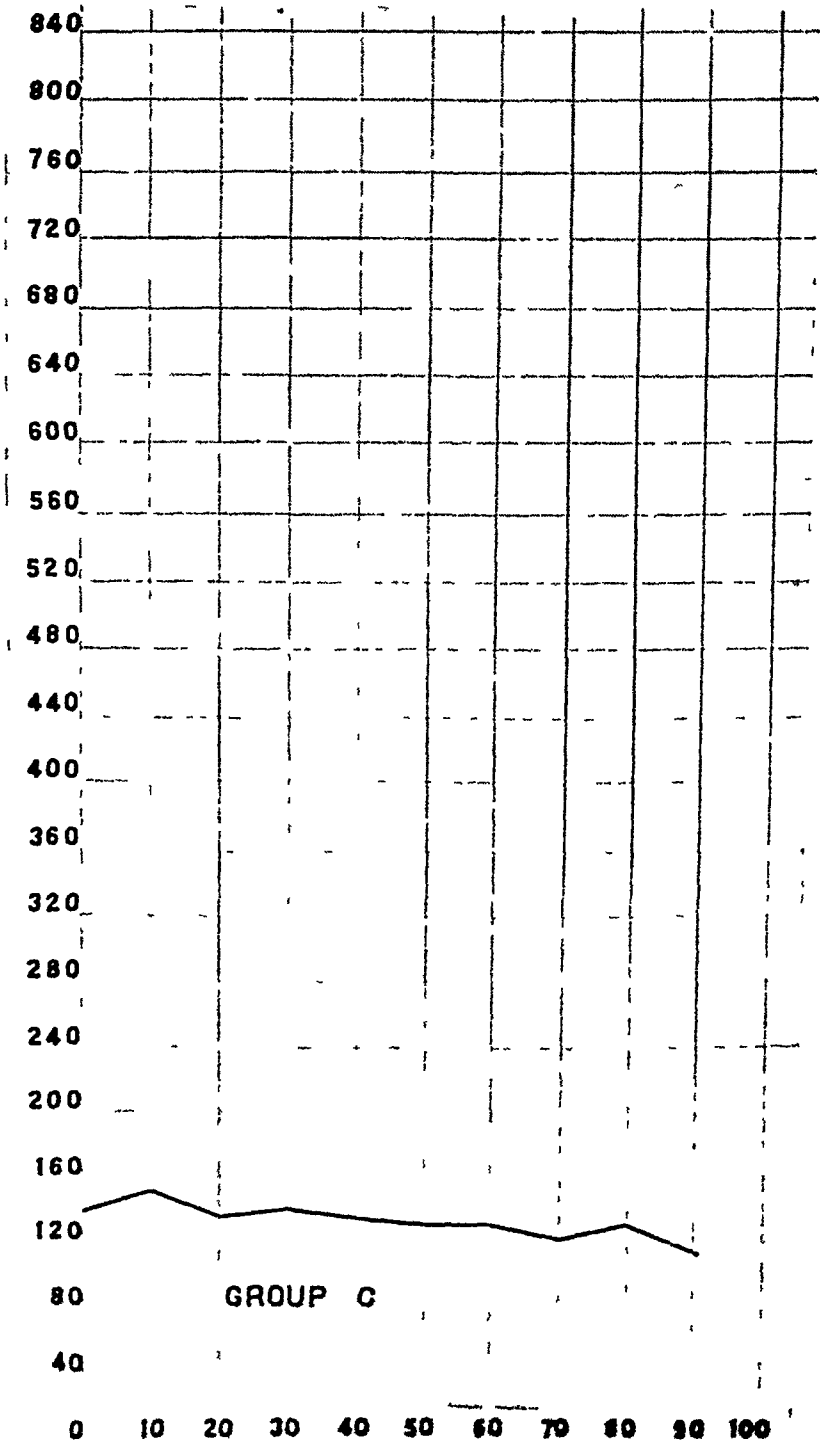


CHART IV



FIG 2 Adrenal cortex of rabbit on high fat diet plus posterior lobe injections  
Note enlargement of glomerular zone, lipoidosis and "exhaustion" appearance

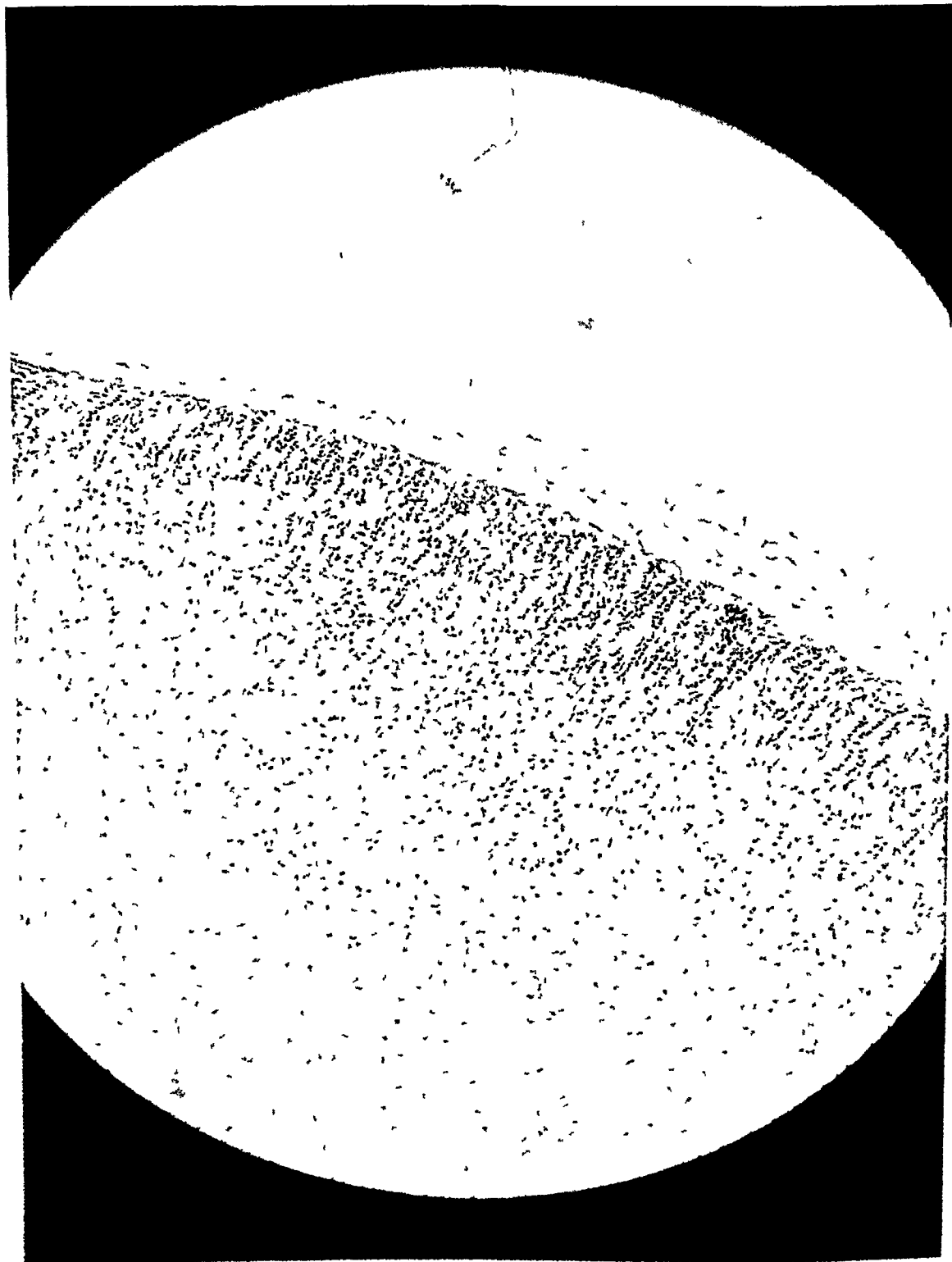


FIG. 3. Normal rabbit adrenal cortex, compare with Figure 2.

ference in suprarenal indexes of the groups is also significant

Group C receiving the injections alone had an average suprarenal index increase over the controls of 15.57 plus, whereas Group B on high fat and injections of the extract had an average suprarenal index increase over Group A on high fat diet only of 16.32 plus

The microscopic examination revealed that the increase of the suprarenals was confined to the cortex. No changes were noted in the medulla (Fig #II and III)

#### STUDIES OF THE AORTA

Studies of the aortae revealed the following

*Control Group* Not one of the control group showed the least suggestion of arteriosclerosis (Fig #IV)

*Group A (High Fat Diet)* Four of the five aortas showed macroscopic arteriosclerotic changes. Illustrative of this is the following as reported by the pathologist, Dr Plinn F Morse

"Aorta shows a few pin point whitish plaques and is scattered over with irregular shaped areas of whitish density producing a somewhat mottled appearance. There is some increase of fat beneath the intima at the exits of the vessels" (Fig V)

It is evident that the high fat diet alone produced arteriosclerosis, thus verifying the work of others



FIG 4 Aorta of control group

*Group B.* This group on a high fat diet plus injections of posterior lobe extract showed the most intense lesions of all. Eight of the ten surviving animals showed arteriosclerosis.

The following report by the pathologist illustrates the intensity of the lesions: "Extensive linear and nodular atheroma distributed densely throughout the course of the aorta. Plaques varying in size from several mm to pin-point around the intercostal arteries" (Fig. VI).

We do not wish to give the impression that every one of this group was as extensive as reported above, but un-

questionably this group showed the most extensive lesions. We submit photomicrographs of the aorta and coronary vessel (Figs VII and VIII), rabbit #57 of this group.

*Group C.* This group on a normal diet and posterior lobe extract injections showed the following results:

Six of the ten aortas were reported as macroscopically normal. Four showed changes suggestive of early arteriosclerosis. These changes were not comparable to Group A on high fat diet alone.

Illustrative of the changes noted is the following report of the pathologist:



FIG. 5

FIG. 6

FIG. 5—Group A, Aorta, high fat diet only.

FIG. 6—High fat diet plus posterior lobe extract—Aorta Group B.

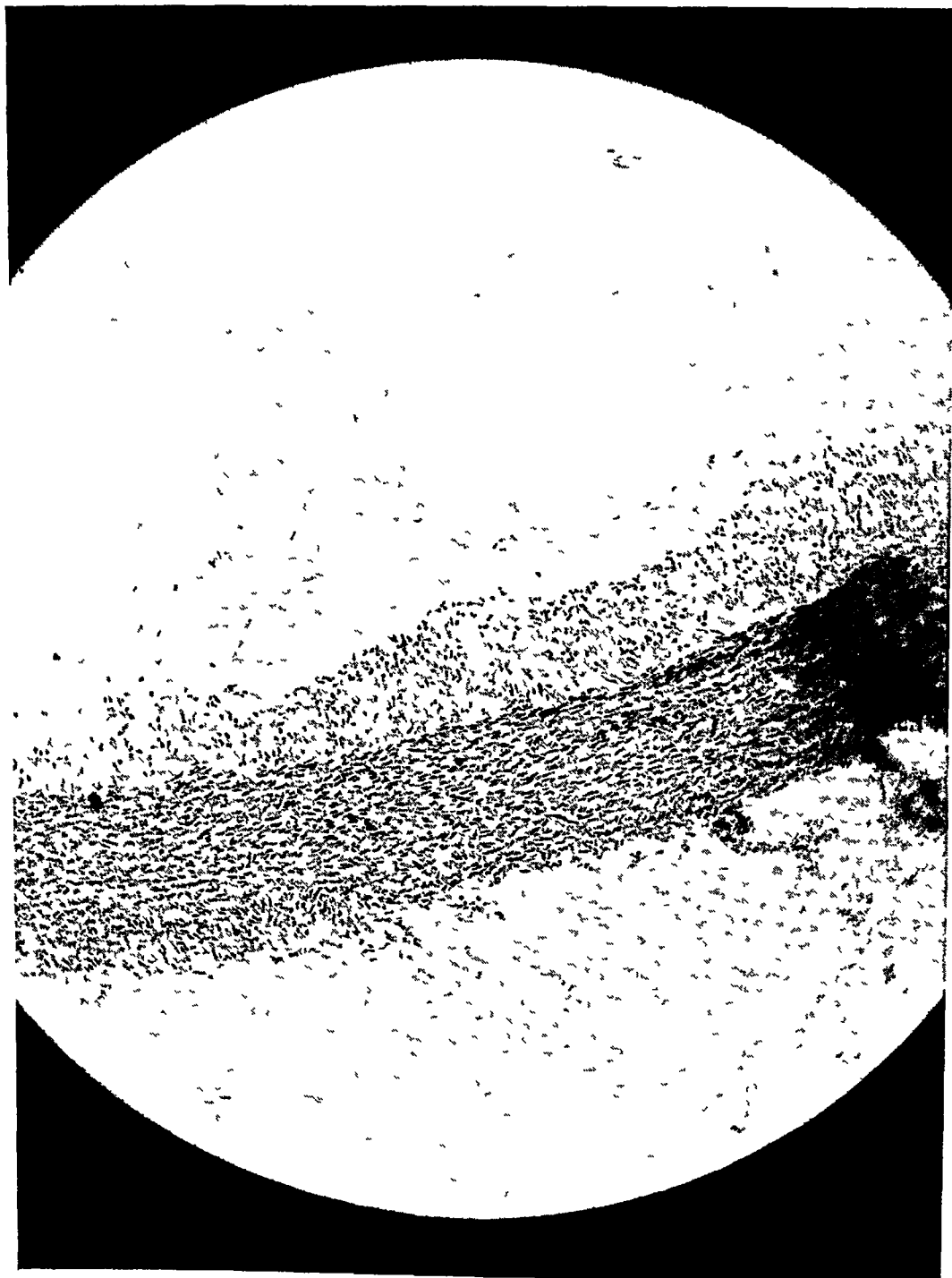


FIG 7 Extensive lipoidosis of Aortic Intima, rabbit aorta—high fat diet plus posterior lobe injections



FIG. 8 Extensive arteriosclerosis. Coronary artery of rabbit, high fat diet plus posterior lobe injections



"Essentially a normal vessel except for diffuse indistinct whitish areas at the cephalic end" (Fig IX)

The average suprarenal weight of this Group C was almost as much as the high fat group, being only 20 mgms less than the latter. The average suprarenal index of Group C was only 1 less than the average of the high fat group.

#### CONCLUSIONS

The importance of suprarenal cortex hypertrophy in arteriosclerosis, hyper-

tension and nephritis makes the suprarenal cortex hypertrophy found in our injected animals of great significance. By the injection of posterior lobe extract alone, without the influence of diet, we are able to produce a suprarenal cortex hypertrophy, an important link in the chain of arteriosclerosis.

Marked production of atheromatous plaques in the rabbit's aorta may be produced within one hundred days by feeding a diet high in cholesterol and the daily injection of posterior lobe pituitary extract.

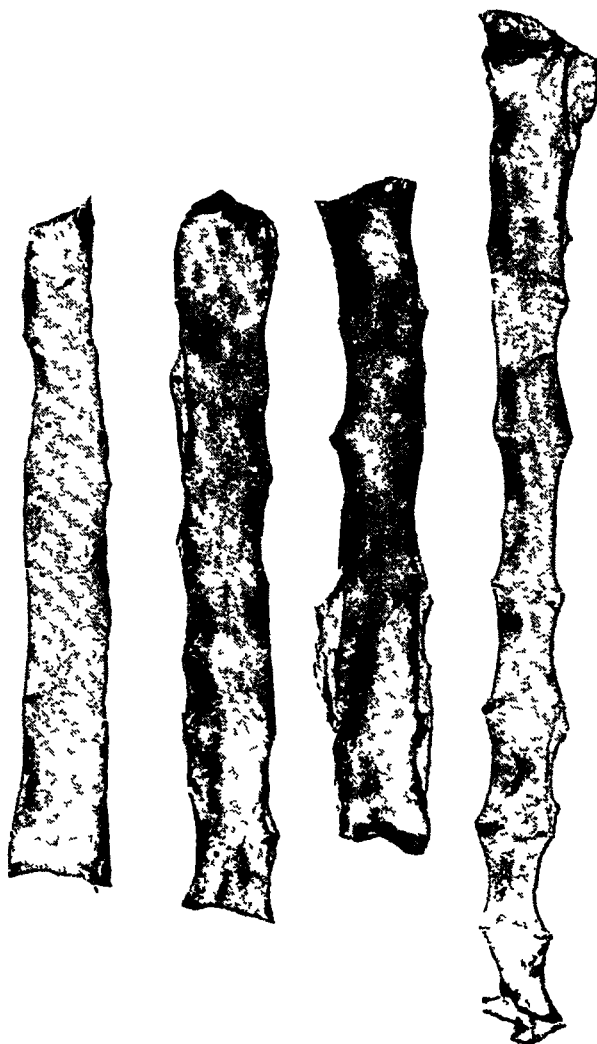


FIG 9 Group C Normal diet plus posterior lobe extract

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# Lower Fat Diet in Diabetes

By JOSEPH H. BARACH, M D , *Pittsburgh, Pa*

**T**HERE are today three distinct views concerning the proper diet in diabetes. One group of workers believes that carbohydrates should be kept at a point believed to represent glucose tolerance of the patient. The second group advocates a high fat, non-ketogenic low carbohydrate diet. The third group, holding the most recent views, advocates what seems like a very high carbohydrate and low fat diet. All agree upon the desirability of avoiding ketosis, meeting caloric needs and supplying the patient with a physiologic diet. It is readily seen that each of these concepts of what constitutes a physiologic diet for the diabetic, differs markedly. Those who give little carbohydrate, believe it advantageous to give small doses of insulin, and the fewer doses per day, the better. Those who allow a high carbohydrate diet are not deterred by the necessarily large doses of insulin. Each of these views is based on presumably good reasons, and satisfactory end results are claimed for the three methods. As the problem stands today, authorities are not in agreement and it is left with the average practitioner to decide for himself as to which is the method of choice. And yet, because of his lesser experience, it is this practitioner who is least qualified to make the decision. This is not a healthy state of affairs, and a unified effort

should be made toward standardization of a treatment for this disease.

## CRITERIA IN TREATMENT

At this point I wish to reiterate certain generally accepted facts, which must be recognized if one is to treat diabetes intelligently and successfully. As far as is known today, these should be considered as actual laws governing treatment of this disease.

- 1 Caloric requirement for adults ordinarily 30 to 35 calories per kilo body weight daily.
- 2 Protein requirement for adults never less than 66 gram and ordinarily 10 gm per kilo body weight daily.
- 3 Blood sugar not to exceed 125 mgm per 100 cc. Avoid glycosuria.
- 4 Sufficient carbohydrate with or without insulin to prevent ketosis.
- 5 Fat carbohydrate ratio. Experience shows that when ratio of fat to carbohydrate exceeds 3 to 1, ketosis will develop. When physiologic proportions of carbohydrate, protein and fat are oxidized, ketosis does not occur.
- 6 Insulin affects and is affected by carbohydrate, protein and fat in the diet, insulin affects the total metabolism.

- 7 Total caloric value of diet and nutritional state, the body weight of patient, should constantly be kept in mind
- 8 The patient should be brought toward normal or slightly below normal weight.
- 9 Where there is acetone and diacetic acid without glycosuria, carbohydrate utilization is too low
- 10 Where there is acetone and diacetic acid with glycosuria, a reduction in fat, protein or carbohydrate or administration of sufficient insulin is imperative

THE NORMAL DIET

Experience has shown that a diet in which 67% of the calories are obtained from carbohydrate, 16% from protein and 17% of the calories from fat is physiologically adequate in health and in disease. In the light of what we have learned from diabetic and other nutritional studies, we know that an individual doing light work will maintain good health at 30 to 35 calories per kilo. Thirty calories per kilo is generally satisfactory for the average diabetic. It may be that the usual American diet is higher in fat than that of the Euro-

pean, because fat is more plentiful here, the reason being economic rather than a special craving or physiologic need for a high fat ration. There are evidences in health and disease which point to the fact that a low rather than a high fat diet is preferable. Believing this to be so, we assume that the same principle should guide our effort of returning the diabetic to a state of comparative health.

APPROACH TO TREATMENT OF THE DIABETIC

When a patient first comes to us we are confronted with the question as to whether the severity of the disease is a useful guide to treatment or whether we should ignore the actual state of the diabetes and attempt to return the patient to a nearly normal diet as quickly as possible. In practice, this amounts to giving a low carbohydrate and high fat diet, or a high carbohydrate and low fat diet with insulin.

VARIATIONS IN PRACTICE

The following table illustrates wide variations in the diet prescription. The figures indicate the diet ordered at the

TABLE I

	Carb	Protein	Fat	Calories
Newburgh and Marsh (Entering Hosp)	27.0 gm	35 gm	170 gm	1778
Graham " "	28	40.6	175	1840
Wilder " "	33	46	192	2011
Campbell " "	40	47	146	1662
Allen " "	45	70	182	2018
Rabinowitz " "	50	50	150	1750
Bartlett " "	50	70	180	2100
Bachr " "	60	48	138	1971
Harrop " "	70	70	171	2050
Kellogg " "	75	40	177	1711
Foster " "	107	70	151	2024
Joshin (When Leaving Hospital)	100	71	132	1925
Barach (Entering Hospital)	116	70	150	2100
Sansom " "	122	62	111	1821
Geyden (Children)	200	100	100	3000

beginning of treatment, for a patient of 70 kilos

From these figures it will be seen that approach to the diabetic problem is highly variable. The carbohydrate ration for the patient of 70 kilos varies from 27 to 288 gm. I know that these values no longer hold good for the present day practice of some of the authors quoted, and that larger carbohydrate rations are now being given.

Low carbohydrate, means likewise a high fat diet. Objections to the high fat diet are many. While there is not as yet an abundance of proof for histologic tissue change brought about by excessive fat in the diet, it is true that such evidence is notably increasing.

On the other hand, there is no question at all concerning the constantly menacing chemical disturbances which follow in the wake of the high fat diet.

Clinically, there is plenty of evidence of disturbances associated with high fat diet in diabetes. Sudden change in character of the food, large amounts of fat, coarse vegetables, roughage and bran are all part of the diet when small amounts of carbohydrate are taken. In my experience, the high fat diet is at times accompanied by epigastric distress, at times real pain. Some patients develop pylorospasm, others have been wrongly diagnosed gall bladder colic and some have attacks of colitis. I have seen these various symptoms disappear completely within a few days, after instituting higher carbohydrate diet. In some there is anorexia, nausea and diarrhea, all of which are discomforting and harmful. With high fat, achylia and diarrhea are not uncommon sequelae. It is also well to think of

mineral deficiencies in a diet too low in carbohydrate foods.

#### CARBOHYDRATE TOLERANCE OF THE PATIENT WITH AND WITHOUT INSULIN

Theoretically, the carbohydrate tolerance of a patient can be estimated by making a few rapid calculations. It is true that this calculation may represent the carbohydrate content of the patient's diet, but the results of this calculation, minus glucose output does not necessarily represent the actual tolerance of the patient for carbohydrates. The total caloric value of the diet as compared with the patient's requirement for that day, and the amount of protein and fat in the diet, are important factors in determining actual tolerance. Likewise the estimated carbohydrate tolerance of a patient when he first becomes sugar free and the estimated tolerance after he has been sugar free for a month, will frequently not be the same at all. This we have known for a long time.

Apparent improvement during the early treatment of a patient does not necessarily indicate renewed pancreatic function or, as some would have us believe, a regeneration in the islands of Langerhans. For such reasons, I believe that reported gains in carbohydrate tolerance frequently are not as real as they seem. To be certain of an increase in carbohydrate tolerance of a patient under laboratory control, one must take cognizance of the patient's weight, the activity of the patient, the total caloric intake and the relative proportions of carbohydrate, protein and fat in the diet. If these conditions are kept nearly constant, and maintained for a suffi-

cient length of time, then the difference between glucose intake and output, will have truer significance

### BODY WEIGHT

This can be successfully controlled in most cases. A group of 142 cases reveals the fact that at beginning treatment 62 were above ideal weight, 78 were below weight and 2 cases were of correct weight. As treatment progressed, 80% of the overweight showed a loss in the direction of the ideal weight, but 20% showed a gain in weight regardless of our effort in that direction. Of the underweight cases 90% were made to gain and 10% showed loss up to the time of these calculations. On the whole, weight control is in the hands of the doctor and presents no difficulties if the patient will co-operate.

### WHEN DOES THE POTENTIAL DIABETIC BECOME DIABETIC?

In 1924 after a study of 375 diabetics, I found that on the basis of 30 calories per kilo, allowing that the normal diet obtained approximately 67% of its calories from carbohydrate, 16% from protein and 17% from fat; only one diabetic in a hundred could take more than half the normal carbohydrate ration. A similar calculation in a group of 97 cases at the present time, shows that 92 out of 97 diabetics had a carbohydrate tolerance of less than 50% of the normal. Eighty-six percent of this group had already lost two-thirds of the normal tolerance when they came for treatment. In another group I find that 130 out of 138 diabetics had a carbohydrate tolerance of less than 150 gram carbohydrate. It is

apparent that most diabetics tolerate less than 150 gram carbohydrate, and only exceptional cases still possess one-half normal tolerance. The majority (86%) of diabetics are down to one-third normal carbohydrate tolerance when they come for treatment. This brings us to the realization that when an individual has lost two-thirds of the normal carbohydrate and other food tolerance, his disease becomes manifest and the patient seeks medical aid.

### APPROACH TO TREATMENT

Under these conditions, which is the course to follow? As already stated, high fat diet offers definite disadvantages both theoretically and practically. High protein diet, higher than 1 gram per kilo for adults is likewise unnecessary. I believe that the majority of healthy city people engaged in ordinary occupations take no more than 1 gram per kilo body weight. I am certain that women take less than 1 gram protein per kilo, daily.

### THE CARBOHYDRATE RATION

This brings us to consideration of the carbohydrates. The important question being, whether we will do well to keep to a low carbohydrate ration which is the common practice today, or whether we will obtain ultimately better results by approaching the normal amount. During the past six years I have kept my patients near the one-third normal carbohydrate when possible and I made effort to avoid insulin. Surveying one group of 100 cases thus treated, I find that there was no change in tolerance in 17, and there was a loss of tolerance in 36 cases and that 17 showed a gain in carbohydrate toler-

ance By a gain in carbohydrate tolerance for this group, I mean the same protein, fat and insulin dosage and greater carbohydrate intake, without glycosuria and hyperglycemia This is not a particularly impressive result The best that can be claimed for it is that these individuals have lived and worked in comfort, and on the whole are going along very satisfactorily Body weight has been controlled in the ideal direction and normal growth has taken place in the young The arteriosclerotic and hypertensive diabetics seem no better or worse than hypertensive non-diabetic patients

#### HIGH VERSUS LOW CARBOHYDRATE DIET

Geyelin was one of the very first to advocate the high carbohydrate diet Sansum's work is well known While my practice has been to allow one-third ( $5/15$ ) normal carbohydrate, one gram protein and fat q s for thirty calories per kilo, Sansum's allowance amounts to three-fifths ( $9/15$ ) of the normal carbohydrate, 0.66 to 1.0 gram protein and fat q s for total caloric requirement

In a group of one hundred and fifty patients, I find that fifty-eight are taking insulin, the average dose per patient is 21.3 units daily Sansum reports an average dose of 42 units daily Considering that my diet contains  $5/15$  and Sansum's diet contains  $9/15$  of the normal carbohydrate it is readily seen why Sansum's patients require twice as much insulin A question of importance is whether on the higher carbohydrate diet, the patient is sufficiently safe against accidents from unexpected hypoglycemia following the use of

large doses of insulin, whether blood sugar can be maintained at a satisfactory level, whether patients will be living more normally, withstanding the wear and tear of life better, and whether they will suffer less deterioration or more, as the years go on These questions have not yet been answered in the affirmative to the satisfaction of all, but it is likewise true that after a larger experience with relatively high carbohydrate diets we may come to the conclusion that it is the better treatment

As shown in Table 1, the diet on which my patient is placed when entering the hospital is higher in carbohydrate than is usually allowed, except by Geyelin for children and Sansum for adults The diet that I have been using (one third normal) contains about half of the carbohydrate allowed by Sansum, for a patient of similar body weight

#### EXCHANGING FAT FOR CARBOHYDRATE

I have chosen for the present study a group of fifty diabetics of nearly all ages, whose diet is being changed to a higher carbohydrate ration Each week the patient adds five or ten gram carbohydrate and subtracts its caloric equivalent in fat We continue this exchange so long as the patients get along with their former dose of insulin and without hyperglycemia or glycosuria The protein is continued at 1 gm per kilo, so that this modification represents a replacement of fat by carbohydrate

Up to the present writing, I find that in one to three months, I have been able to increase the carbohydrate in amounts varying from ten to seventy-five gm,

the average increase being 42 gram, all of which indicates that previously estimated carbohydrate tolerance was too low. Some have had the large carbohydrate ration for a short time only and have not yet reached their full capacity for this exchange. Twenty percent of the cases found it necessary on their own initiative to temporarily increase the insulin dosage seven units per day. In a number of these, increase was coincidental with acute colds. Sixteen percent reduced their insulin 4 units per day. In two cases insulin was entirely eliminated. The others required no change of insulin. Seven patients lost a total of eleven pounds, the equivalent of 14 pounds each, twelve gained a total of forty-five pounds, the equivalent of 37 pounds each. I am satisfied that these patients are better off for the change in diet, they feel better and as far as I can see, they are better in every way.

THE REFRACTORY DIABETIC

There is a group of diabetics which have in the past been difficult to treat because of their inconstant response to diet and insulin. On the same diet and insulin dosage these patients were sugar free one day and had a high glycosuria and hyperglycemia the following day. At times they were suspected of cheating and at times we felt that such responses could only be due to nervous strain or nervous unbalance, whatever that might be. The fact remained that we could not control them with three and in some cases with four doses of insulin per day. These outstanding cases, some of which had been under my care five or six years, under the newer regime with lower fat diets,

have settled down to being "ordinary" diabetics, instead of being in the throes of hyperglycemia in the morning and hypoglycemia at night, they are now free of such irregularities and are under satisfactory control. I believe that their refractory state was due to the high fat in the diet. It is apparent that with the high fat ration large quantities of insulin was used up in an irregular fashion. For these patients, the low fat diet with its proportionate higher carbohydrate ration has been of great benefit.

ORDERING THE DIET METHOD

By the following procedure I find that we determine the patient's diet more quickly than by subjecting them to a period of undernutrition, followed by a gradual return to maintenance diet. With this procedure, I have never seen any ill effects and the stay in the hospital is shortened. Tables 2 and 3 give the normal weight for children and adults.

TABLE II

NORMAL WEIGHT—6 MONTHS TO 17 YEARS				
Height	Age		Weight	
			Male	Female
46 in	6	mos	18	—
47 in	8	mos	20	—
48 in	10	mos	21	—
49 in	1	yr	22	—
50 in	1½	yr	25	—
51 in	2	yr	27	—
52 in	2½	yr	30	—
53 in	3	yr	32	—
54 in	3½	yr	34	—
55 in	4	yr	36	—
56 in	5-7	yr	37	—
57 in	5-8	yr	40	—
58 in	5-9	yr	42	—
59 in	6-11	yr	44	—
60 in	7-12	yr	46	—
61 in	7-13	yr	48	—
62 in	8-14	yr	50	—
63 in	9-15	yr	52	—
64 in	10-16	yr	54	—
65 in	11-17	yr	56	—



TABLE III

## NORMAL WEIGHT 17 TO 34 YEARS

Ages	17—19	20—24	25—29	30—34
Height	M—F	M—F	M—F	M—F
4' 10"	109—1	115—4	120—6	123—6
4' 11"	111—1	117—4	122—6	125—6
5' 0"	113—1	119—4	124—6	127—6
5' 1"	115—1	121—4	126—6	129—6
5' 2"	118—1	124—4	128—6	131—6
5' 3"	121—1	127—4	131—5	134—6
5' 4"	124—1	131—5	134—5	137—5
5' 5"	128—2	135—6	138—6	141—5
5' 6"	132—2	139—6	142—6	145—5
5' 7"	136—2	142—5	146—6	149—5
5' 8"	140—2	146—5	150—6	154—6
5' 9"	144—3	150—5	154—6	158—6
5' 10"	148—3	154—5	158—6	163—8
5' 11"	153—3	158—5	163—8	168—10
6' 0"	158—3	163—6	169—10	174—12
6' 1"	163—3	168—6	175—12	180—14

## NORMAL WEIGHT 34 TO 54 YEARS

Ages	35—39	40—44	45—49	50—54
Height	M—F	M—F	M—F	M—F
4' 10"	125—5	128—4	130—3	131—2
4' 11"	127—5	130—4	132—3	133—2
5' 0"	129—5	132—4	134—3	135—2
5' 1"	131—5	134—4	136—3	137—2
5' 2"	133—4	136—3	138—2	139—1
5' 3"	136—4	139—3	141—2	142—1
5' 4"	140—4	142—3	144—2	145—1
5' 5"	144—4	146—3	148—2	149—1
5' 6"	148—4	150—3	152—1	153—1
5' 7"	152—4	154—3	156—1	157—0
5' 8"	157—5	159—4	161—2	162—0
5' 9"	162—6	164—5	166—3	167—1
5' 10"	167—8	169—7	171—5	172—2
5' 11"	172—10	175—9	177—7	178—4
6' 0"	178—13	181—12	183—10	184—7
6' 1"	184—16	187—15	190—13	191—10

Female weight, subtract number of pounds designated. See Conversion Table

Table 4 is a conversion table, pounds to kilos, the use of which reduces calculation for the prescribing physician to a minimum

Table V gives the normal diet for all ages. It is given here for comparison. We use these values as our guide in the treatment of nutritional disturbances, cardio-vascular disease, essential hypertension, nephritis and in other diseases. This is a safe diet and well within physiologic values.

Table VI indicates gram per kilo diet, for the diabetic.

## PROCEDURE

1 According to age and height of patient, multiply gm Carbohydrate, Protein and Fat by the number of kilos

TABLE IV

## CONVERSION TABLE

Body Weight	Body Weight	Body Weight
Lbs	Kilo	Lbs
15.4	7	83.6
17.6	8	85.8
19.8	9	88.0
22.0	10	90.2
24.2	11	92.4
26.4	12	94.6
28.6	13	96.8
30.8	14	99.0
33.0	15	101.2
35.2	16	103.4
37.4	17	105.6
39.6	18	107.8
41.8	19	110.0
44.0	20	112.2
46.2	21	114.4
48.4	22	116.6
50.6	23	118.8
52.8	24	121.0
55.0	25	123.2
57.2	26	125.4
59.4	27	127.6
61.6	28	129.8
63.8	29	132.0
66.0	30	134.2
68.2	31	136.4
70.4	32	138.6
72.6	33	140.8
74.8	34	143.0
77.0	35	145.2
79.2	36	147.4
81.4	37	149.6
151.8	69	151.8
154.0	70	154.0
156.2	71	156.2
158.4	72	158.4
160.6	73	160.6
162.8	74	162.8
165.0	75	165.0
167.2	76	167.2
169.4	77	169.4
171.6	78	171.6
173.8	79	173.8
176.0	80	176.0
178.2	81	178.2
180.4	82	180.4
182.6	83	182.6
184.8	84	184.8
187.0	85	187.0
189.2	86	189.2
191.4	87	191.4
193.6	88	193.6
195.8	89	195.8
198.0	90	198.0
200.2	91	200.2
202.4	92	202.4
204.6	93	204.6
206.8	94	206.8
209.0	95	209.0
211.2	96	211.2
213.4	97	213.4
215.6	98	215.6
217.8	99	217.8
220.0	100	220.0

2.2 lbs = 1.0 Kilo

TABLE V

## DIET PER KILO BODY WEIGHT IN HEALTH

Age	Gm Carb	Gm Prot	Gm Fat	Calories
to 4 yrs	10.0	3.0	3.10	80
4—10 yr	10.0	1.5	2.66	70
10—17 yr	7.5	1.5	2.66	60
17—25 yr	5.0	1.5	2.10	45
Adult	5.0	1.0	0.66	30

TABLE VI

DIABETIC DIET PER KILO BODY WEIGHT  
CARBOHYDRATE ½ NORMAL

Age	Gm Carb	Gm Prot	Gm Fat	Calories
to 4 yrs	3.3	3.0	3.3	55
4—10 yr	3.3	1.5	3.4	50
10—17 yr	2.5	1.5	3.2	45
17—25 yr	1.67	1.25	2.0	40
Adult	1.67	1.00	2.14	30

which represents the desired body weight for that patient. Table VI is based on one-third normal carbohydrate, 1 gm protein and sufficient fat to meet caloric needs.

2 When patient is sugar free three days, add 10 gm carbohydrate and deduct 4.5 gm fat from total diet. Repeat

this until hyperglycemia or glycosuria appears

3 If patient cannot take this (1/3 normal diet) without glycosuria, insulin is advisable

4 If patient shows hyperglycemia or glycosuria, give insulin before breakfast. If that is insufficient, give second daily dose before evening meal. In exceptional cases when necessary, give third daily dose before luncheon. Allow one unit insulin for each 2 gm glucose output.

5 If patient can take one-third normal diet or more, without hyperglycemia; more carbohydrate and insulin is optional with doctor and patient.

6 After patient has been sugar free for one month, try substituting carbohydrate 10 gm for fat 45 without changing insulin. Continue this exchange toward the normal diet unless hyperglycemia or glycosuria appears.

7 If tolerance is improving, increase of carbohydrate or reduction of insulin is again optional with doctor and patient.

#### SUMMARY

Numerous workers in this field are agreed that high fat diets are undesirable and it is assumed that only the smallest amounts of fat which will meet the caloric needs of the patient should be prescribed. At best, the fat in the diabetic diet always exceeds normal values. Although it has been my practice to allow a generous amount of carbohydrate, I find that by a progressive exchange of fats for carbohydrates, patients seem to take care of considerably more carbohydrate than was formerly allowed. In a comparatively short time this exchange has permitted an increase of 10 to 75 grams carbohydrate per day. This exchange has been welcomed

by the patient in every instance. My experience with this group of fifty patients leads me to believe that the larger carbohydrate ration is an advance in diabetic therapy.

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# Linseed Meal Sensitization\*

By GRAFTON TYLER BROWN, B S , M.D , F A C P , *Washington, D C*

**A**LTHOUGH occasional references to flaxseed or linseed sensitization are scattered through the vast literature on allergy, it seems to me that hypersensitiveness to this substance is deserving of further emphasis

## REVIEW OF THE LITERATURE

Contact with ground flaxseed, in the preparation of flaxseed poultices, has been known to produce urticaria of the hands and arms, and also asthmatic attacks Walker<sup>1</sup> reported one case of angioneurotic edema caused by flaxseed

Cooke<sup>2</sup> referred to one patient with asthma and coryza from linseed, and testing this patient intradermally with linseed extract produced an immediate constitutional reaction manifested by asthma, coryza, urticaria, and also angioneurotic edema of the neck lasting two days This experience illustrates the danger of testing intradermally with such a potent allergen as linseed, especially when there is a positive or suspicious history of allergic symptoms from inhalation or ingestion of this substance Cooke also mentioned flaxseed as giving another patient asthma

Meyer<sup>3</sup> reported the case of a man, complaining of asthma, who two years before consulting him had gone on a farm to raise chickens Shortly after taking up that work he noted that attacks of shortness of breath accompanied his working about in the dust of straw, alfalfa, or chicken feed There was complete cessation of symptoms when he was away from the farm His asthma was more marked in the winter On the first visit, negative intradermal tests were obtained with feathers, cereals, hay, straw, and cow epithelium At the request of his physician he had brought with him samples of feeds and powders from the farm, and from these, extract solutions were prepared On the second visit, he was tested with them, and markedly positive reactions were obtained with two, namely, a poultry powder and a scratch feed The most marked reaction of all, however, was elicited with an extract of flaxseed Extracts of house dust, orris, and animal danders gave negative reactions On the third visit, he reported that among other offending feeds he had gotten rid of one poultry tonic containing 70 per cent flaxseed Relief was prompt, and when last seen he reported continued general good health, interrupted by only infrequent and mild attacks in cleaning out the

\*Presented at the Sixth Annual Meeting of the Society for the Study of Asthma and Allied Conditions, Atlantic City, N J, May 3, 1930

chicken house. He continued, of course, to avoid flaxseed feeds.

In testing 293 patients having allergic dermatitis, Piness and Miller<sup>4</sup> obtained positive reactions to flaxseed in nine patients, but in only one, a druggist, could they say that this substance was more than a possible contributing cause of the allergic dermatitis.

Nicholson<sup>5</sup> discovered seven cutaneous reactions to flax and linen in testing 158 patients with a series of from 125 to 150 proteins. He stated that these reactions would have been missed with a small series of tests. The cutaneous scratch was used for testing, and the reactions were all very marked. They were equally marked when a small amount of linseed meal, dissolved in a drop of deci-normal sodium hydroxide was rubbed into a scratch. Only one of these seven patients, a farmer, volunteered the information that he was hypersensitive to flax. I will abstract Nicholson's reports of these seven cases.

*Case 1*, was a young man of 28 who had suffered from very severe attacks of asthma since he was 5 years of age. Protein sensitization tests showed the following positive reactions: flaxseed + + + +, chicken feathers + + +, and mild or doubtful reactions to a number of other substances. The offending substances were removed from his diet and surroundings, but the attacks continued with their usual severity. After a month's trial of the above desensitization by injections of a protein extract of flax and chicken feathers was tried. The first dose was 0.1 cc. of a 1 to 50,000 solution. Little or no reaction occurred, but after the third dose, which was increased according to schedule, a most violent anaphylactic attack occurred. It began with tingling of the ears and extremities. Later there was almost total suffocation, cyanosis, and a drop

in the blood pressure. Ten minims of 1 to 1,000 adrenalin was immediately given hypodermically, and the attack passed off in a few minutes. Both the patient and the doctor were so alarmed that they did not wish to try any further injections. This patient was last heard from two years later and still had attacks of asthma, as severe as ever.

Personally, I consider it poor therapy to mix unrelated substances for hyposensitizing injections. Furthermore, there can be no definite schedule for increasing the doses, as each patient is a law unto himself.

*Case 2*, was a man 27 years of age who had suffered from asthma for 21 years. The attacks were frequent and severe from December to March, but never occurred in summer. A slight eczema was present in childhood. This lesion still occurred between his fingers in winter. Protein sensitization tests showed a very marked reaction to flax only. When questioned after the test, he remembered having an unusually severe attack of asthma after eating "Roman Meal", a breakfast food which contains flaxseed. Flax desensitization was diligently carried out over a period of four months. The first injection of 0.1 cc. of 1 to 10,000 extract produced a very severe attack of asthma. A more dilute solution was used for a while, and the amount gradually increased. At times slight attacks of asthma occurred and the dose would be decreased. After four months' treatment, the injection of 0.8 cc. of 1 to 15,000 would produce very slight asthma. The patient thought his asthma was slightly less troublesome than before treatment. The dermatitis between his fingers disappeared. Two years later he said he still had asthma in cold weather and on exertion, but it was of a different character and somewhat less severe than what he had suffered before the injections. The diameter of the wheal produced by flax protein rubbed into a skin scratch was three quarters of the one which had occurred on the original test before treatment was begun.



Close view of a panicle of flax, showing buds, flowers, and bolls in successive stages of growth, some of the latter being fully matured

The fact that this man had asthma only in the period from December to March might be explained by a bacterial factor, but on the other hand, the thought occurred to me that possibly it could have been due to his drinking milk from cows fed on dairy feed containing linseed meal. In other words, during the summer the cows would be out on pasture, where as in the winter they would be given dairy feed exclusively, and consequently the milk from these cows would contain linseed protein in the winter but not in the summer. This patient's experience with "Roman Meal" demonstrated conclusively that the ingestion of flaxseed protein was capable of producing severe asthma. The constitutional reaction from the first injection of the flax protein extract could, in all probability, have been avoided by first testing the patient with various dilutions to determine the proper initial dose.

Case 3, was a woman 35 years of age who had suffered from rhinitis and seasonal hay-fever for twenty years. Protein sensitization tests showed the following positive reactions: flaxseed + + + +, horse hair + + + +, orchard grass + +, rye + +, daisy +. Later intradermal tests showed the following reactions: flaxseed extract 35 cm in diameter, new linen extract 3 cm in diameter, old linen extract 16 cm in diameter, silk extract 0.5 cm in diameter. About an hour after these intradermal tests a severe attack of sneezing developed. No treatment was undertaken at that time, but the following spring a mixture of equal parts of flaxseed, horse hair, orchard grass and rye pollen was prepared and injections given. This patient said that she obtained a fair degree of benefit from two such courses of prescribed treatment.

I feel obliged to again criticize the mixed or "shotgun" treatment. Where

it is necessary to treat with unrelated substances, these treatments should be given separately.

Case 4, was a nurse 35 years of age who for the preceding eleven months had had violent attacks of sneezing and lachrymation, which came on almost every morning after she had visited the store room. Protein sensitization tests showed the following positive reactions: flaxseed + + + +, chamois +, cheese  $\pm$ . After four injections of the flax protein extract, starting with 0.1 cc of 1 to 10,000, the attacks of sneezing ceased, and had not returned when she was last heard from, nearly three years later. Dr. Nicholson did not have an opportunity of testing out the cutaneous reaction to flaxseed after the injections, but he judged from the result in Case 2 that it would have been unchanged.

Nothing is said about what was kept in the store room, but the fact that this patient was a nurse makes me think of the possibility of her having come in contact with flaxseed, which is commonly used in the preparation of poultices.

Case 5, was a man 58 years of age who had suffered from asthma for a year. Protein sensitization tests showed a very marked reaction to flaxseed only. As treatment, a 1 to 1,000 solution was made up and given by mouth, starting with one minim in water three times daily after meals and increasing every third day by one minim. He took this treatment over a period of three months, but noticed no change in his attacks of asthma. These attacks were intermittent and occurred in about the same frequency and severity as before treatment.

Case 6, was a farmer 35 years of age who had suffered from asthma of a very severe type for seventeen years. When questioned regarding the causative factor, this patient stated, "I never know when the asthma comes on, but I know it is by the time I get to bed at night." He was given a course of treatment with flax protein extract, and the asthma was completely relieved.

left his farm and worked on the railroad for a winter, and during that time he was entirely free from asthma. Protein sensitization tests showed the following positive reactions: flaxseed + + +, buckwheat + +, dog hair + + +, horse hair + + + +, cow hair + + + +, goose feathers +. A mixture of 1 to 10,000 each of flax, dog, horse and cow hair, and goose feathers was prepared for his treatment. A drop of this mixture in a scratch on his arm produced a large urticarial wheal. A 1 to 100,000 solution was prepared, and as his reaction to this solution in a scratch was scarcely noticeable, he was given 0.1 cc subcutaneously. The amount of the injection was slowly increased every second day. After the 0.4 cc dose of 1 to 100,000 he had slight asthma. The dose was decreased, and no constitutional reactions developed after that. He had no attacks of asthma during a period of a month while he was in the hospital for observation, and he would have continued taking the injections in increasing doses over a period of about six months, but a week after returning to his farm he died of a virulent pneumonia, following exposure to cold.

In addition to my opposition to the mixed treatment, I do not consider that the desensitizing injections should have been given as often as every second day.

Case 7, was a boy 4 years of age who had had asthma for the preceding two years. Protein sensitization tests showed a + + + reaction to flax and also marked positive reactions to a number of other substances. The boy's parents were advised to eliminate from his diet and environment all of the foods and other substances to which he gave positive reactions, but insufficient time had elapsed to know the result.

In a preceding paper<sup>6</sup>, I stated that sensitization to linseed meal, a common component of poultry feed, is one of the rather unusual causes of hay-fever and asthma.

Rowe<sup>7</sup> reported the case of a man, aged 38, who had had an itching ec-

zema on his face, neck, arms, and legs, for three years, appearing each spring and becoming extremely severe by September. Whenever he left his chicken ranch, the eczema would immediately improve. Skin testing gave three plus reactions to *artemisia vulgaris* and *biennis*, to *ambrosia psyllostachya*, and to flaxseed, which was in the chicken mash he was using.

Feinberg<sup>8</sup> stated that flax and its products are occasionally responsible for allergic conditions.

Figley and Elrod<sup>9</sup> reported thirty cases of asthma known to have been caused by the inhalation of finely powdered castor bean dust in the neighborhood of a linseed and castor oil mill. Five of these thirty patients also gave cutaneous reactions of varying strengths to flaxseed, but these were regarded as examples of multiple sensitization, especially as the castor bean reactions so markedly overshadowed the flaxseed reactions.

Thomas<sup>10</sup>, under the heading of Flax, writes as follows:

"Flaxseed, when ground into meal and inhaled, is a possible cause of asthma. It is, however, but seldom used in the modern household except in making poultices. A flaxseed poultice upon the skin of a patient sensitive to its proteins might well be the cause of allergic symptoms. It is also possible that linseed oil may contain enough protein to account for symptoms in a sensitive person exposed to it, as, for example, a painter or occupant of an apartment whose walls have been freshly oil painted. Flax protein for testing and treatment is available for use in cases where sensitiveness to linen is suspected."

Balyeat<sup>11</sup> in an article on perennial hay-fever stated that he had found one patient whose symptoms were very much increased on working with





was no fever, coryza, or conjunctival irritation. The disturbances lasted in all about two hours, and cleared up without any lasting ill effects. Because of the similarity between this and the first case, cutaneous tests, with the same technic, were made with wheat, rye, flax, and flaxseed. The reactions to wheat, rye, and flax were negative, but flaxseed caused a very strong reaction which appeared within five minutes, at which time the excess test solution was removed. However, the reaction continued to spread, many long pseudopodia appearing. A wheal which measured 4 cm in diameter was present at the end of fifteen minutes. The whole flexor surface of the forearm was erythematous.

At the age of 18, this patient had had a severe infection of the foot, which was treated with flaxseed poultices for about two months. Shortly after his recovery from this infection, he began to have sharp attacks of asthma, which would appear and leave suddenly. When he was about 38 years old, he had had an attack somewhat similar to the one described, but milder, which came on several hours after he had eaten buckwheat cakes.

Black concluded that flaxseed apparently causes more violent local and general reactions in the hypersensitive than do most of the other allergic food substances, and that in these two cases there was a history of previous contact with flaxseed in the form of poultices, from which an inference as to the etiology of the hypersensitiveness might be drawn.

#### FLAX AND ITS PRODUCTS\*

\*In preparing this section I have drawn freely from such authoritative sources as Henry and Morrison's book "Feeds and Feeding", and various bulletins of the U. S. Department of Agriculture.

*Flax Plants* Flax is the common name for plants of the genus *Linum* and for the fiber obtained from the stems of *L. usitatissimum*. This

species, of unknown origin, has been in cultivation from a very remote period. The plant is an annual, with slender stems and blue flowers. Fiber flax and seed flax belong to the same botanical species (*Linum usitatissimum*), but, like sweet corn and field corn, they are of different types. Seed of fiber flax must be sown in order to produce fiber-flax plants, and vice versa. A fiber-flax plant has the characteristic tall stalk (about 3 feet) and few seed bolls, whereas a seed-flax plant has shorter stalks (about 2 feet) and many seed bolls. The flax boll contains ten seeds, when all develop. The cultivation of flax for fiber and the cultivation of flax for seed or oil are two distinct industries. For 138 years flax has been grown in the United States, principally for its seed. The invention of the cotton gin in 1792 and the consequent cheap production of cotton fiber practically ended the flax-fiber industry in this country. Seed flax in the United States is grown chiefly in North Dakota, Minnesota, South Dakota, and Montana, ranking in production in the order named.

*Flax Fiber* This ranks next to cotton in importance among the vegetable fibers. The straw of seed flax grown in the Northwest does not yield a fiber suitable for spinning. Approximately 80,000 tons of flax straw are used in the United States each year in the manufacture of insulating material, tow for upholstering, and coarse wrapping cord. It is also used at times as feed for livestock. Fiber flax yields both spinning fiber and seed suitable for sowing, oil production, or feeding. The preparation of spinning fiber from flax straw is a process in-

volving skilled labor and special machinery After harvesting the flax, the various operations are known as threshing, retting, breaking, scutching, and hackling The flax fiber is spun in the flax-spinning mills to make sewing thread, shoe thread, harness thread, fishlines, fish nets, and twines

*Linen* Linen thread or yarn is woven to make the various linen materials, the most important of which are art linen, batiste, bird's eye linen, cambric, collars and cuffs, damask, diaper, dress linen, fire hose, glasscloth, handkerchief linen, huckaback, lawn, linen crash, sheeting, shirting, table linen, and toweling Lint is a flocculent material procured by raveling or scraping linen, which is sometimes used for wadding and batting, or for dressing wounds and sores

*Flaxseed* The seeds of the flax plant are small, flat, oblong, brown seeds Although the terms flaxseed and linseed are used more or less interchangeably, some authorities wisely prefer to limit the term flaxseed to the seed of the flax plant prior to the expression of the oil, and use the term linseed only to designate the products of the seed, namely, oil, cake, and meal

For ten years previous to 1909 the United States produced a surplus of flaxseed, and considerable quantities were exported to Europe From 1909 to the present, however, flaxseed production in the United States has averaged slightly less than half of the consumption, and in recent years large quantities have been imported from Argentina and Canada

Analyses of mature flaxseed show it to contain from 30 to 45 per cent of

oil, and an average of 22.6 per cent crude protein Flaxseed also contains a hydrocyanic-acid-producing glucoside which, when acted upon by an enzyme in the seeds, yields the poison, prussic acid On account of the high commercial value of the oil it contains, flaxseed is rarely used for feeding stock other than calves Dairy calves are made sick at times by feeding them flaxseed which has been allowed to stand in the presence of water, thus permitting the enzyme to act and produce free hydrocyanic acid Some authorities deny this, stating that the trouble is due to an admixture of some poisonous seed such as the castor bean Nevertheless, an analysis of flaxseed made very recently at the office of the Food, Drug, and Insecticide Administration of the U. S. Department of Agriculture showed it to contain 650 parts of HCN per 1,000,000 Therefore, in making gruel or mash from untreated flaxseed, it is advisable to use boiling water and keep the mass hot an hour or two, to destroy any prussic-acid-forming enzyme in the seed

In medicine, flaxseed is used as a demulcent and an emollient. Its infusion, flaxseed tea, is used internally in catarrhs of the respiratory mucous membrane, in enteritis and dysentery, and in irritation of the kidneys or the urinary passages Flaxseed poultices are quite commonly used in the treatment of localized inflammation

"Roman Meal" is stated by its manufacturers, the Roman Meal Company of Tacoma, Washington, to be a balanced food made from whole berries of wheat and rye, with bran and sufficient especially prepared lactose, etc.

seed to neutralize by its healing properties the irritating effect of bran upon the lining of the digestive tract. I have been told that there is an identical or similar preparation put out by a Canadian concern.

"Flaxolyn", a proprietary laxative manufactured by the Herbal Flaxolyn Corporation of Brooklyn, N. Y., is said to contain, among other things, baked flaxseed as a demulcent and local soothing agent. This same company also markets an emulsion containing flaxseed.

*Linseed Oil* The oil of the flax seed is either extracted by the "old process", through crushing and pressure, as in the production of cottonseed oil, or by the "new process" in which it is dissolved out of the crushed seed with naphtha, the residue in either case being variously termed linseed oil meal, linseed meal, or simply oil meal. Flaxseed yields about  $2\frac{1}{2}$  gallons (18 $\frac{3}{4}$  pounds) of oil to a bushel (56 pounds) of seed. Oil produced from immature seed is a greenish brown, while that from ripe seed has a yellowish brown color. Ripe seed produces a greater amount of oil as well as a finer quality. Linseed oil is used extensively in the manufacture of paints and varnishes, linoleum, oilcloth, printers' ink, patent leather, imitation leather, oilsilk, and many brands of furniture polish.

*Linseed Cake and Meal* The residue left after the oil has been extracted is known as linseed cake or, if ground, as linseed meal. One bushel of flaxseed (56 pounds) produces about 37 $\frac{1}{4}$  pounds of linseed cake. Practically all linseed meal, especially in the United States, is made by the

"old process". Old-process linseed meal contains approximately 34 per cent of crude protein and 6 to 9 per cent of fat or oil, whereas new-process meal carries an average of 3 per cent more crude protein but contains only 2 to 3 per cent of fat or oil. The prussic-acid-forming enzyme in flaxseed is destroyed by the heat to which the ground seed is ordinarily subjected in both the old and the new process of oil extraction. There is no more healthful feed for limited use with all farm animals than linseed cake or meal, with their rich store of crude protein, slightly laxative oil, and mucilaginous, soothing properties. Linseed meal is one of the most popular feeds for dairy cattle, and is also a common ingredient of poultry feeds. It is excellent for horses, and is also one of the best protein-rich supplements for fattening sheep and beef cattle, and gives good results with swine when fed in proper combination. In this country the demand is chiefly for linseed meal instead of the unground cake, probably owing to the fact that, mixed with other concentrates, it is fed mostly to dairy cows.

A linseed solution is quite commonly used in beauty parlors to hold the hair in place after it has been waved.

### CASE REPORTS

Without searching through my case-record files, I can recall several patients with typical linseed meal sensitization, and I will briefly report these cases.

*Case 1* A young woman, aged 29 years, was referred to me in June, 1922 with bronchial asthma of four years' duration. Her attacks started with violent sneezing. During the attacks, her eyes itched severe-

ly and became swollen. When I questioned her carefully, she told me she believed that at least one of her attacks had been caused by an orris root shampoo. A cutaneous test with orris root protein gave a marked positive reaction, and all other skin tests were essentially negative. She was advised not to have any more orris root shampoos, and to avoid using powders or other cosmetics containing orris. Also, she was given orris root desensitization. As a result, the asthma promptly left her and she remained entirely free for a period of four years.

This patient consulted me again in February, 1927 with asthma which had recurred about two months before. She stated that she was still avoiding orris root in all forms. During the four year period which had elapsed since I first treated her, she had married and moved to the country where they raised their own chickens. They fed the chickens a prepared mash, which she said made her sneeze when she handled it. The mash was found to contain wheat bran, cocoa shell meal, linseed meal, alfalfa meal, meat meal, and powdered milk. A cutaneous test was made with each of these ingredients and they were all negative with the exception of linseed meal, which gave a definitely positive reaction. It is interesting to note that a skin test with a commercial flaxseed protein gave only a doubtful reaction. Tests with chicken feathers and other substances were all negative with the exception of orris root, which still gave a positive reaction although it was definitely smaller than when I first tested her. This patient's asthma disappeared after eliminating the chicken mash containing linseed meal, and when last heard from she was still perfectly well.

*Case 2* A man, 34 years of age, consulted me in October, 1926 with perennial hay-fever. He had terrible itching of the eyes, sneezing, running of the nose, and headaches, and recently had developed some coughing and wheezing. The discharge from his nose was thin, clear water. He was a carpenter by trade, but had always lived in the country and been around chickens. He had never had any of this trouble while away from home or at work. He fed the

chickens mash, which he had noticed would make him sneeze. The mash contained alfalfa meal, meat meal, middlings, bran, linseed meal, ground oats, and corn meal. He was tested cutaneously with each of these ingredients and gave a marked positive reaction to linseed meal, the other components being negative. In this case also, a skin test with a commercial flaxseed protein gave only a doubtful reaction. Skin tests with chicken feathers and various other substances were all negative. This patient's non-seasonal hay-fever left him just as soon as he discontinued using a chicken mash containing linseed meal.

*CASE 3* A woman, 55 years old, was brought to me in September, 1929 with bad asthma and non-seasonal hay-fever of about 15 years' duration. With the attacks, her eyes, nose, and face got very red and swollen, and she sneezed and wheezed a lot. She thought that drinking milk made her worse. These attacks made her terribly nervous, and at times were accompanied by headache, nausea and vomiting. She lived on a farm and in this connection stated that she could not go around chicken feed, and that flax also bothered her. A cutaneous test with linseed meal gave an enormous reaction, the urticarial wheal being about 2 inches in diameter. Tests with commercial flax and flaxseed proteins gave only a doubtful reaction to the former, but a marked, positive reaction to the latter. Skin tests with a large number of other substances showed her to be multiple-sensitive, but none of these other reactions could compare with the one to linseed meal, which remained plainly visible on her arm for several days after the test. Tests with milk proteins were completely negative, but it is perfectly possible that she had been getting linseed protein in the milk, as linseed meal was used routinely in their dairy feed. The chicken feed they used also contained linseed meal. I advised the discontinuance of all feed containing linseed, and in addition decided to give this patient linseed treatment, for its specific as well as non-specific desensitizing effect. A 1 to 20 extract was prepared by adding 5 grams of linseed meal to 100 cc of Coca's fluid 17. After this

extract was Berkefeld filtered and examined for sterility, 1 to 200, 1 to 2,000, and 1 to 20,000 dilutions were prepared, using Coca's fluid as diluent. When I tested her with these dilutions, she gave a positive reaction to the 1 to 2,000, and a practically negative reaction to the 1 to 20,000. Treatment was started with 0.05 c.c. of the 1 to 20,000 extract, and the dose was gradually increased at weekly intervals. After taking only ten injections, this patient was so well that she discontinued treatment, and when heard from very recently, reported that she was entirely free of all symptoms of asthma and hay-fever.

I have three other patients under my care at the present time, who give marked, positive, cutaneous reactions to linseed meal. One of these patients has a dermatitis and seems to be sensitive only to linseed. The other two have chronic perennial asthma, and are both multiple-sensitive. These three patients have not yet been sufficiently studied, to determine the clinical importance of their sensitization to linseed meal, but it is interesting to note their lack of reaction to skin tests with commercial flax and flaxseed proteins. The patient with dermatitis gave no reaction to flax protein, and only a slight or doubtful reaction to flaxseed protein. One of the patients with asthma gave no reaction to flax and only a slight reaction to flaxseed, but gave a definitely positive reaction to my linseed meal extract. The other patient with asthma gave no reaction to skin tests with commercial flax and flaxseed proteins, and yet gave definitely positive reactions to cutaneous

tests with "Roman Meal", "Flaxolyn", and my linseed meal extract.

### SUMMARY

The vast literature on allergy contains occasional references to sensitization to flax, flaxseed, or linseed, and these references are reviewed somewhat completely.

A general description of flax and its products is given to show the numerous ways in which a person hypersensitive to the flax proteins may come in contact with them.

Several typical cases of linseed meal sensitization are reported by the writer.

### CONCLUSIONS

Although sensitization to flaxseed or linseed is one of the less commonly encountered forms of hypersensitivity, it is of sufficient importance to merit careful consideration in diagnosing and treating asthma, non-seasonal hay-fever, dermatitis, or urticaria, especially in persons such as farmers or nurses, who come in contact with these substances.

Sensitization to the protein of flaxseed or linseed is usually very marked, and the best method of detecting it is by means of the cutaneous or "scratch" test, using ordinary linseed meal and moistening it with a drop or two of tenth-normal sodium hydroxide solution.

Specific desensitizing injections of a linseed meal extract may be given with perfect safety, providing sufficient care and judgment are used in determining the initial and subsequent doses.

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# Avitaminosis Complicated by Cestodiasis; Case Report\*

By J A McINTOSH, M D , F A C P , *Memphis, Tenn*

**A**VITAMINOSES occur in man and other animals when diets poor or deficient in vitamins are eaten, but attention to protozoa and metazoa as "Vitamin robbers" in the intestinal tract capable of inducing avitaminosis in the host if the diet is below normal therein has not been recognized and given emphasis

We are familiar with the saying that a good appetite in the presence of malnutrition is suggestive of tape worm infestation, and such metazoa as the broad tape worm of the fish and the hookworm are known to cause secondary anemias, but they are not generally regarded as "Vitamin robbers" inducing the diseased state of avitaminosis. We have seen individuals harboring metazoa and protozoa with signs and symptoms, mild to severe, of avitaminosis and it has caused us to regard them as "Vitamin robbers" and to place emphasis upon the association of the infestation and the disease state.

Proof that metazoa and protozoa require vitamins for growth and reproduction is being sought by feeding experiments in the laboratory at the St Joseph's Hospital. Some of the protozoa have been cultured with success by

us in media containing water soluble vitamins. We have used a culture of the *Waskia intestinalis* to determine the growth promoting and reproducing rate in blood serum, urine, spinal fluid, saliva, and liver extract, and have observed marked variations. We found a lesser rate of growth in urine from individuals with mild avitaminosis than in normal urine. From this it would seem that such an animal could be used to determine the quantity of growth promoting vitamin in any given fluid. Certainly an accurate test is desirable to quickly determine mild avitaminosis in man before it is written on the face (See picture)

The established distinction of vitamins into A B C D and E groups detectable when absent in diets by causing signs and symptoms referable to epithelial, nervous, endothelial, osseous, and reproductive tissues is of service in selecting diets for treatment of xerophthalmia, beriberi, scurvy, pellagra, rickets, and sterility, but the need of early diagnoses in the human is obvious. According to Statt<sup>1</sup> the albino rat is the most suitable animal in testing for vitamin A, the pigeon or chicken for B, the guinea pig for C, the cat or puppy for D, but so far as we know the *Waskia intestinalis* has not

\*Read before the Memphis and Shelby County Medical Society April 15, 1930

been utilized for such tests before. We have tested certain commercial foods labeled concentrated vitamins with the *Waskia intestinalis* using water soluble vitamin B from the Irish potato as control solution. We expect to report data at a later date.



FIG 1 *Avitaminosis (Pellagra) Complicating Cestodiasis*. Repeated feces examination showed ova of *Hymenolepis nana* (tapeworm). Observe the characteristic symmetrically distributed eczema of pellagra on face (band like), forearms, and dorsal aspect of hands and feet. Note the anxious expression.

If Cestodes, as do higher forms of animal life, require vitamins for growth and reproduction, they obtain them from the food in the host, and the host, as suggested by the following case report of associated infestation and the state of avitaminosis.

Baby L. A., white female, age  $2\frac{1}{4}$  years, was admitted to the St. Joseph's Hospital on 5/15/29 to the service of Dr. K. M. Buck, complaining of an eruption on face, neck, hands, and feet. She is the youngest of six children of a poor family in Arkansas. Her mother, whom she nursed up to three weeks prior to admission to the hospital, died of childbirth complications. The father noticed small multiple eruptions on her neck at this time. These gradually became confluent and spread and were crusted as shown in the accompanying photograph. Her diet before admission consisted of pregnant mother's milk, corn bread, dried beans, Irish potatoes, and salt pork meat. None of the other children was similarly affected and all subsisted on the same diet except mother's milk. There had been no previous illness except measles at one year of age.

The physical examination revealed an erythematous, brownish, moist crusted eruption as stated in the complaint with brownish staining of the adjacent skin. The facial expression was stoic, and she was not responsive to sympathetic advances. There were fourteen well developed teeth, and the tongue was clean, red and shiny. The hair and skin were dry and lacked normal lustre. The balance of the examination revealed nothing abnormal. The bony skeleton was not X-rayed. Her admission weight was 19 9/10.



pounds, and the departing weight 22 $\frac{3}{4}$  pounds. During the hospital stay of 56 days the temperature was never over 100 degrees Fahrenheit. Between 5/15 and 6/1 we made eight total white and differential leukocyte counts averaging 17,000 with eosinophils 32%, neutrophils 60%. One hundred defecations were charted and of these forty were examined microscopically. Ova of the *Hymenolepis nana* (see fig 31) were found constantly up to 5/28/29 and none thereafter though the specific

worm medicine was not given until 7/1/29. Charcot Leyden crystals were present in the stool examined 6/11/29. The blood flocculation test for syphilis was negative. The urine was negative except for acetone bodies upon admission.

Due to the absence of atrophic lesions one medical consultant said that the condition was not pellagra. Another stated that it was pellagra with atypical features.

The diet fed at the hospital was com-



FIG 2 *Avitaminosis (Pellagra) Complicating Cestodiasis* A posterior view of patient

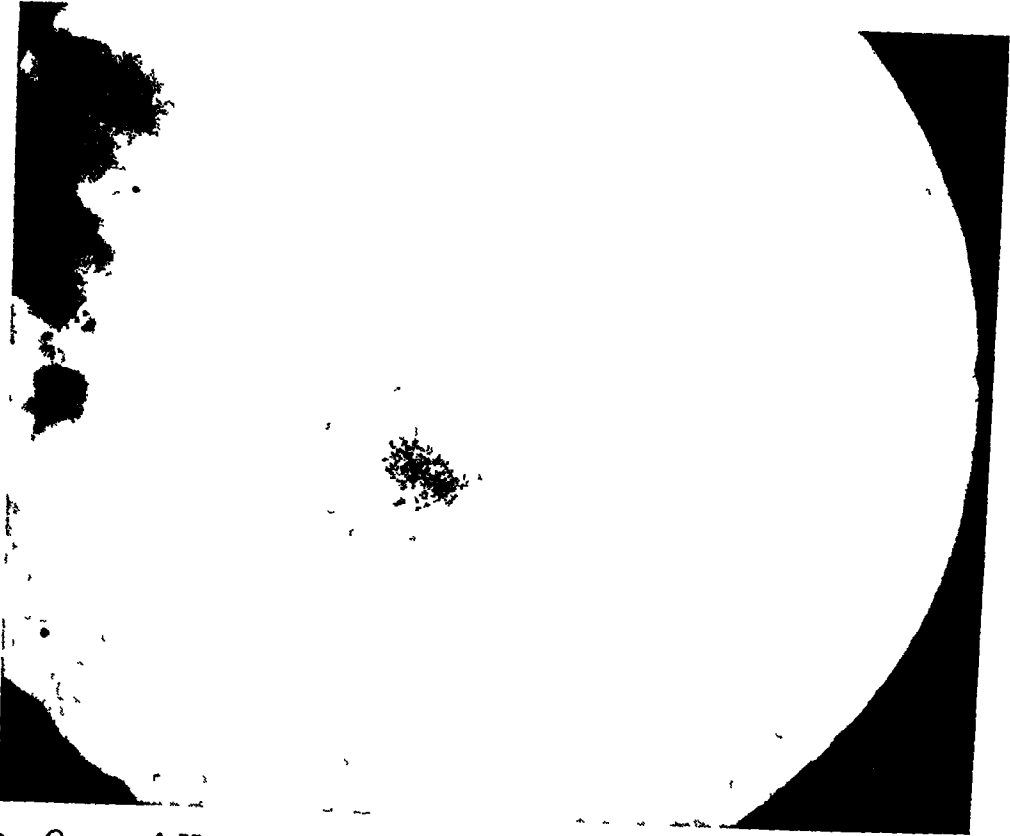


FIG 3 *Ovum of Hymenopelis Nana* Present in feces of Baby L. A, 16mmx10 magnification

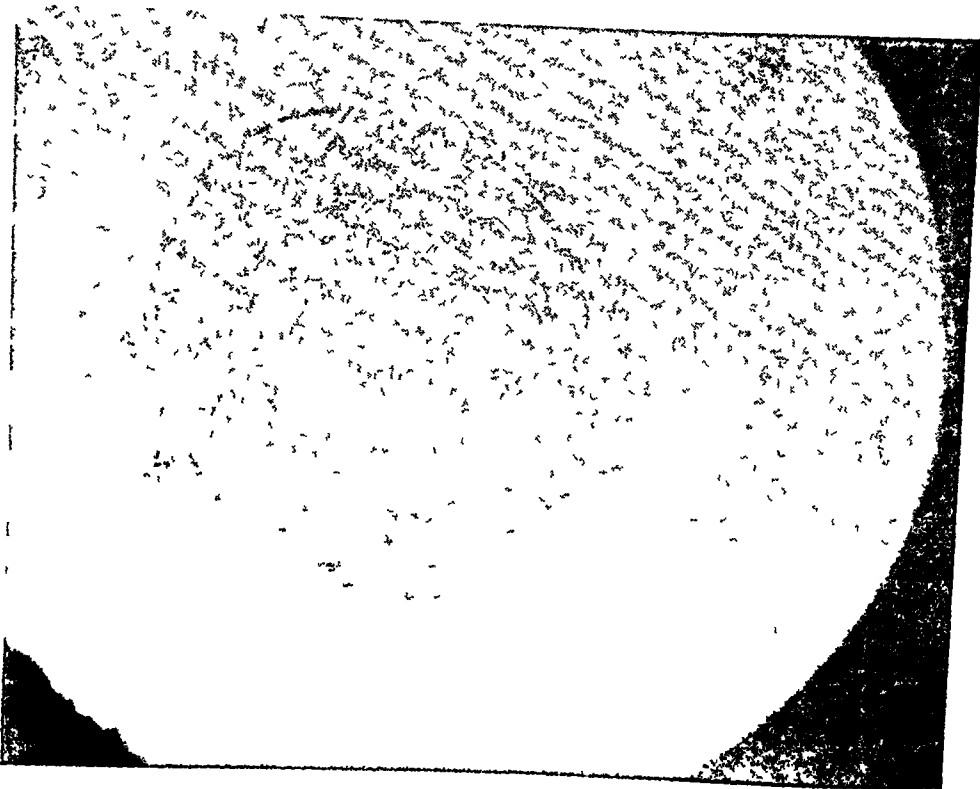


FIG 4 *Ovum of Hymenopelis Nana* Present in feces of Baby L. A, 4mmx10 magnification

posed of broth, cereals, sweet and buttermilk, cocoa, vegetable soup, custard, orange juice, crackers, jello, rice, spinach, potatoes, eggs, peas, and chicken. Olive oil was applied locally to eruption. Eight grains of sodium cacodylate were given in 16 sub-cutaneous doses. Brewer's yeast and cod liver oil labeled vitamins A, B, C and D were given t.i.d. Definite improvement followed the ingestion of maltine with cod liver oil. Calomel, aspidium, magnesium sulphate, and tea enemas were given, the latter to eradicate the taenia though the ova had disappeared from the stools following the concentrated vitamin diet. The anterior and posterior view photographs indicate the improvement fourteen days after admission.

The adult worms were not found though repeated search of the stools were made.

#### DISCUSSION

The ova found in the feces correspond to the description of the dwarf tapeworm *Hymenolepis nana*. This parasite, according to Simon<sup>2</sup>, may cause loss of appetite and diarrhea, and in some instances, epileptic convulsions. A similar parasite has been found in rats and are regarded by Hall<sup>3</sup> as identical to ones found in the human. Development in the human takes place in the intestinal canal. The young worm leaves the egg, enters a villus of the mucosa and in 62 hours develops into mature bladder worms (cysticeroid form). This breaks and the liberated worms attach themselves to the mucosa and become adult worms (Strobiliata forms) in two weeks. The adult is 4-8 mm long with a bell shaped head set with 24-28 hooklets. The segments are yellowish and are four times as broad

as long and contain colorless round and oval eggs having an outer and inner envelop. They measure 68 micra in diameter. The oncosphere with hooklets are within the inner capsule. The ova of other cestodes do not have the outer capsule and the transparent material between. The common hosts are children.

The type of avitaminosis present in this case report corresponds to vitamin

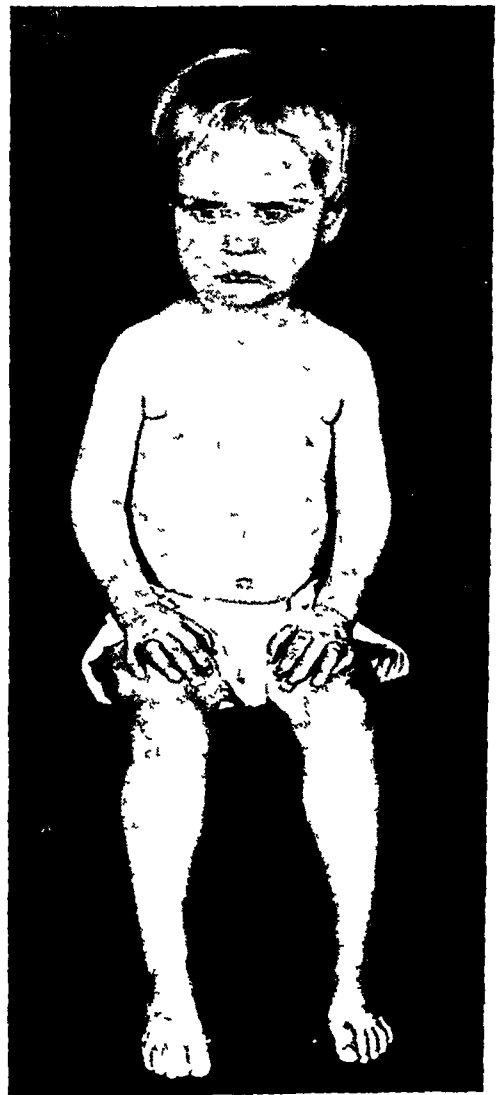


FIG 5 *Avitaminosis*. Two weeks after treatment with foods rich in Vitamin "B". Note increase of animation in face and residual stains from eczema.

B complex deficiency or pellagra. Vitamin B complex or the growth promoting vitamin is water soluble and contains fractions separable by heat. The heat labile fraction is anti-neuritic and is called vitamin F or B-1. The heat stable fraction is called vitamin G or B-2 or anti-pellagic. Deficiency in the diet of the heat stable fraction of vitamin B causes retardation of growth, loss of weight, soreness of eyes, mouth, nose, weakness, and lethargy. Diarrhea is common. With less deprivation skin symptoms are more prominent with bilateral symmetrical positions such as were present in Dr. Buck's patient.

"The rapidity with which symptoms of vitamin B deficiency becomes apparent indicates that the body has only a limited capacity for storing this vitamin." We cannot explain why diets reinforced with concentrated vitamin B caused the ova to disappear from the stools in this patient. A similar observation has been made in flagellosis (*Chilomastix mesnili*). At first they increase, then diminish in the feces after a diet of yeast fed several weeks.

#### CONCLUSIONS

Because of the frequent association of mild to severe avitaminosis in indi-



FIG 6 (*Avitaminosis*) Posterior aspect two weeks after treatment with foods rich in Vitamin "B"

viduals harboring metazoa and protozoa and the clinical improvement following administration of concentrated vitamins and the ready growth in artificial media containing water soluble extracts, we therefore regard them as "vitamin robbers" and capable of inducing certain deficiency diseases such as pellagra

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# Tetralogy of Fallot: Report of a Case With Bacterial Endocarditis of the Pulmonary Valve and Collapse of Both Lungs\*

By ROY S LEADINGHAM, M.D, F A C P, *Atlanta, Ga*

**A** WELL developed and well nourished intelligent white female child fifteen years of age with cyanosis of face and extremities, entered the hospital June the first complaining of dyspnea, nausea, and vomiting. She stated that she had been cyanotic all her life, but more since an attack of influenza the preceeding Christmas. Dyspnea, which formerly had been present only after unusual exertion, also became more distressing after this illness. For six months previous to admission to the hospital, she had had repeated attacks of swelling of face and extremities, and received treatment for kidney trouble because of the presence of albumin in her urine.

Her family history was negative, and previous illnesses included measles, mumps, chicken pox, whooping cough, and pneumonia. Her tonsils had been removed when she was ten years of

age. Her father stated that she was a full term baby, began walking and talking at the usual time, and attended school with others of her age until the onset of her last illness.

She was a well developed child resting quietly in bed in no apparent discomfort. Her temperature was 96 F; pulse 90, regular and of good volume; and respiration 18. Her blood pressure was 120/80. There was extreme cyanosis of face and extremities and moderate clubbing of fingers and toes. Her pupils reacted equally to light and accommodation. The retinal vessels were engorged and tortuous, but no hemorrhages were present. The cervical glands were not enlarged.

A broad diffuse cardiac impulse was visible over the precordium, and there were visible pulsations of the superficial veins of the chest and neck. PMI was 10cm to the left of the midsternal line in the fifth interspace. LBD was 13cm and RBD 4cm from the midsternal line. There were no palpable thrills. To the left of the sternum the first sound of the heart was partially replaced by a moderately rough, blowing systolic murmur, maximal in the

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From the medical service of the Georgia Baptist Hospital and the Department of Medicine, Emory University, School of Medicine.

Illustrations by Dr P F Lineback, Dept of Micro-Anatomy, Emory University, School of Medicine.

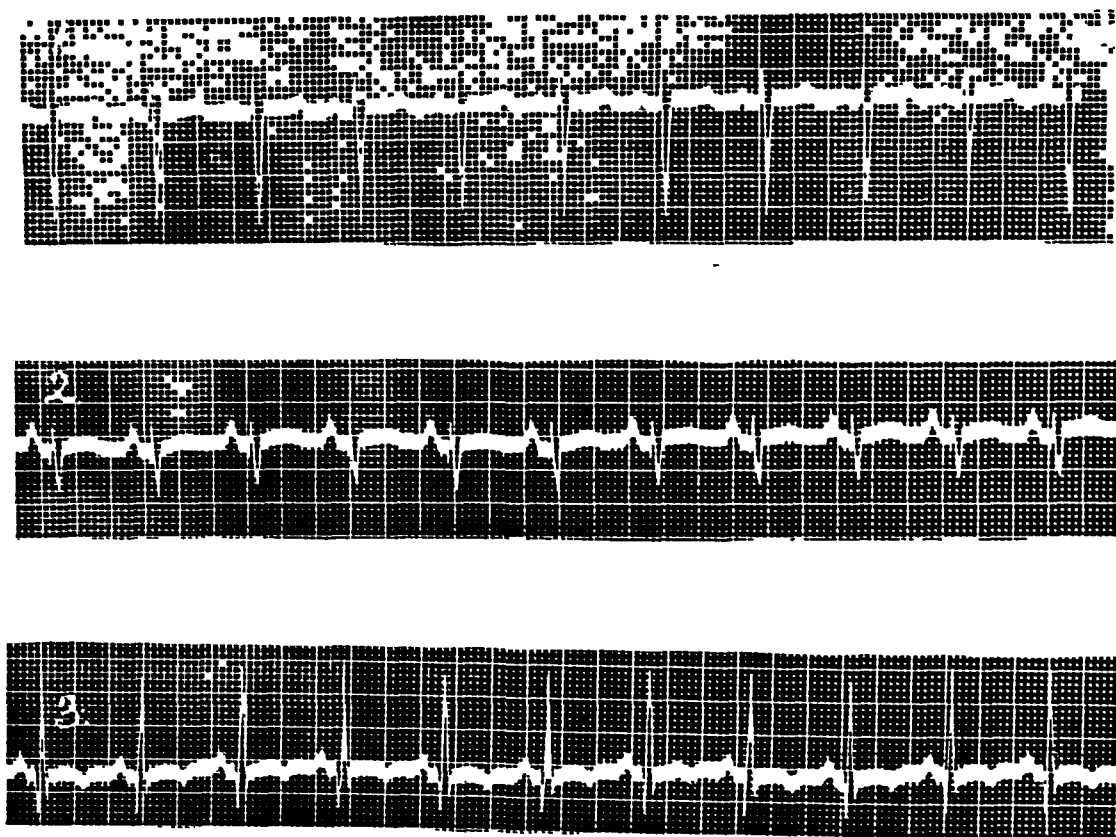


FIG 1 Electrocardiogram showing right axis deviation (Dr J. E. Paullin)

3rd and 4th interspaces. It was transmitted to the left midclavicular region but not to the vessels of the neck. Liver dullness extended from the right fourth interspace to 4 cm below the costal border.

Teleo of the heart at seventy-two inches showed the following dimensions according to the Bardeen scale, median right 3 cm, median left 10.5 cm, oblique 14.5 cm, aortic arch 5 cm, greatest transverse of heart 13.5 cm, greatest transverse of chest 22.5 cm. In the left oblique position, the retrocardiac space was obliterated by the enlarged heart. The electrocardiogram recorded right axis deviation.

For the first three months in the hospital her temperature rarely reached normal and varied from 96 to 98 F.

Two blood cultures were negative. There was 50 mg non-protein nitrogen, 25 mg urea nitrogen, and 2 mg creatinin in 100 cc of blood. Blood viscosity was 11. Bleeding and coagulation times were normal. Urinalyses were at all times negative except for large amounts of albumin in all specimens. On admission, the red blood count was 6,000,000 and hemoglobin 100 (Sahli). With no apparent change in her general condition, dyspnea and cyanosis gradually increased and two months after admission the red cell count reached 10,910,000 and hemoglobin 130. Because of dyspnea and cyanosis, she was given oxygen two or three times daily and about two weeks later, on August 12th, the cell count had gradually decreased to 8,590,000.

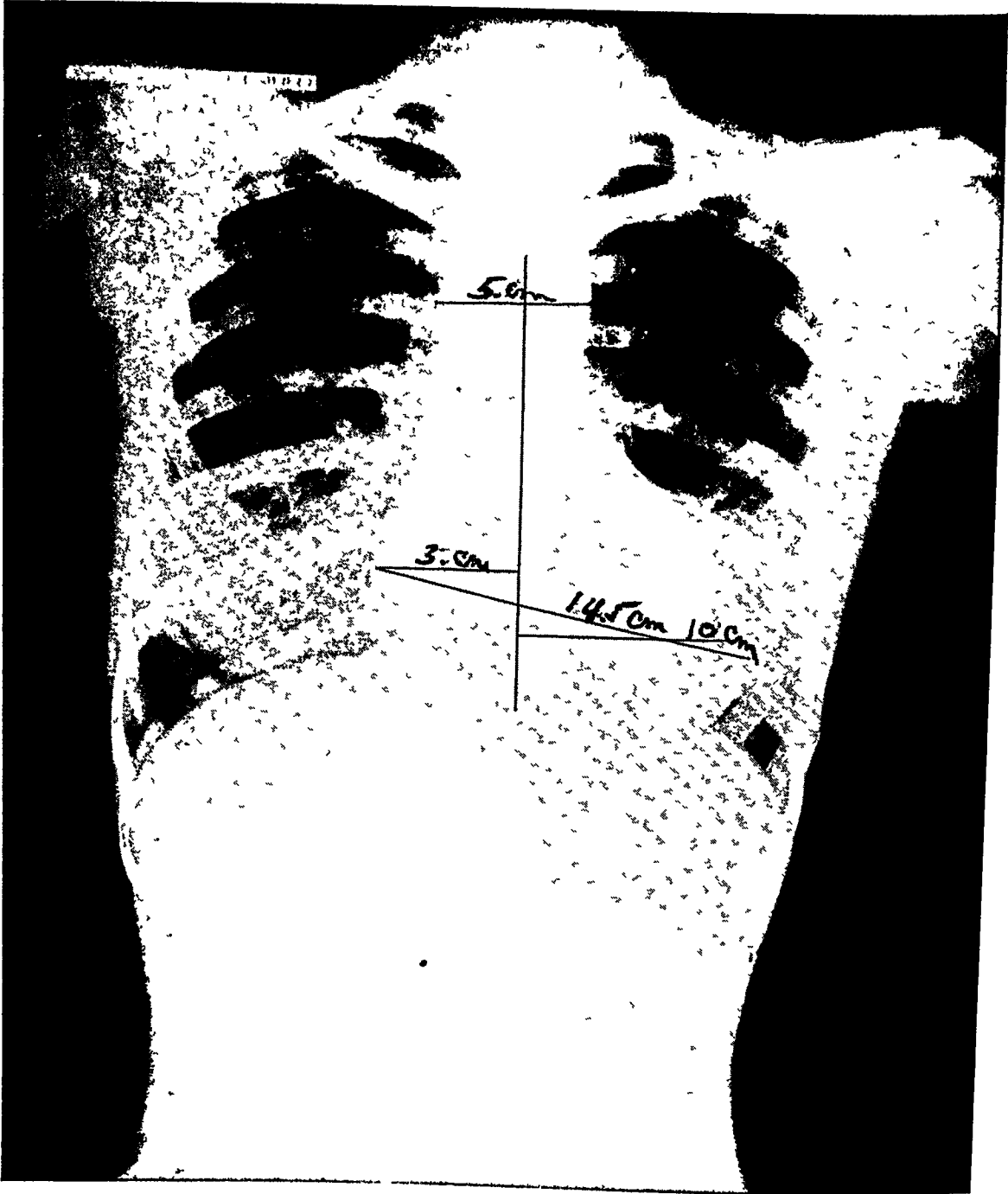


FIG 2



and hemoglobin 107 At this time, there were only 2,850 leukocytes with neutrophils 45%, small mononuclears 50%, eosinophils 3%, and basophils 2% Shortly thereafter she suffered an attack of acute heart failure Her pulse became very weak, rapid, and irregular and she was very dyspneic Oxygen was discontinued She was digitalized and afterward received two grains of digitalis daily until a few days before her death On August 21st, the red cell count was 9,840,000 and hemoglobin 120 There were 5,550 leukocytes Oxygen was resumed because of dyspnea and ten days later there was a decrease of only 100,000 red cells but the leukocytes were down to 2,650 At this time there was 85mg of non-protein nitrogen in 100 cc of blood

Early in September her temperature became a little higher and varied from 96 to 99.6 F For ten days she frequently coughed up blood streaked sputum and was occasionally nauseated Her face, including eyelids, became swollen and her extremities very cold She was more cyanotic and had great difficulty in breathing Shortly after this attack she seemed very much better and improved so rapidly that she wanted to get out of bed She sang, read, and said that she felt better than at any previous time in the hospital This feeling of well being lasted about a month She had few brief periods of dyspnea relieved by oxygen which was then given only when indicated for her comfort At one time the red cell count reached 12,000,000, but during the month of October varied between 9,000,000 and 10,000,000 Early in November she became listless and drowsy She spat up blood streaked sputum

more frequently Dyspnea and cyanosis also increased

On the day of her death, November 11th, she awoke in the morning feeling quite well Her temperature was 98 F, pulse 100 regular and of good volume, respiration 20 At 11 40 A M she had a sudden attack of dyspnea and called for oxygen which gave her some relief At 2 00 P M her pulse was 120 and respiration 22 She was more cyanotic At 5 45 P M respiration was 28 and pulse 120 At 5 55 P M she ceased to breathe

The clinical diagnosis at the time of death was congenital heart disease with septal defect and pulmonary stenosis

An autopsy was performed an hour after death and showed collapse of both lungs and passive congestion of liver and spleen Culture from the hearts blood after several days incubation showed no bacterial growth

The heart weighed 328 grams It was quite spherical in shape and the apex was on the right side of the septum The greatest transverse diameter was 10 cm, of which 6 cm was right ventricle The right auricle was larger than the left There were two left and one right pulmonary veins The aortic valve measured 5 cm, mitral valve 7 cm, tricuspid valve 10cm, and the pulmonary valve 2 cm The pulmonary valve had two cusps upon which was a vegetative lesion that practically occluded the lumen of the pulmonary orifice About 2 cm beyond the valve there was a similar though smaller lesion upon the wall of the pulmonary artery The right ventricle measured 1.5 cm and the left 2 cm in thickness The foramen ovale was patent and 3mm in diameter In the region of the pars

## Roy S. Leadingham

membranaceum there was a large septal defect 3 cm in diameter, bounded below by the upper margin of the interventricular septum 7mm in thickness and above by the opening of the aorta which received blood from both the right and left ventricles. It was separated from the pulmonary orifice by a thick muscular wall 1 cm in thickness which extended downward 3 cm from the pulmonary valve and with the anterior ventricular wall formed an infundibulum 3mm in diameter leading from the right ventricle into the pulmonary artery. Interest in congenital heart disease has been recorded in many observations upon single and combined malformations of the heart, with and without endocardial infections and other associated anomalies. Peacocks "Treatise on Malformations of the Human Heart" was the first clinical and pathological review of the subject in the English language. After his death, his collection became the property of

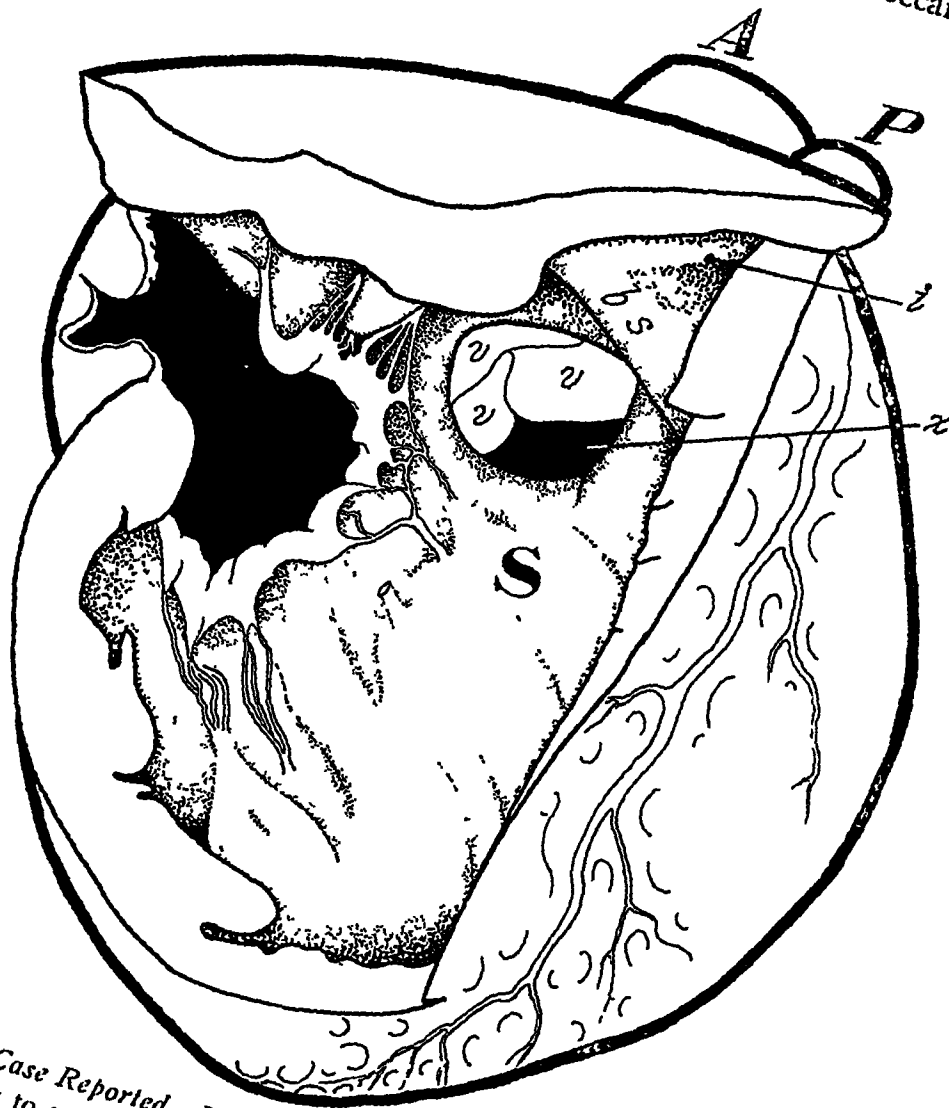


FIG. 3 Heart of Case Reported. X—interventricular septal defect b s—bulbar septum i—infundibulum leading to pulmonary artery from right ventricle

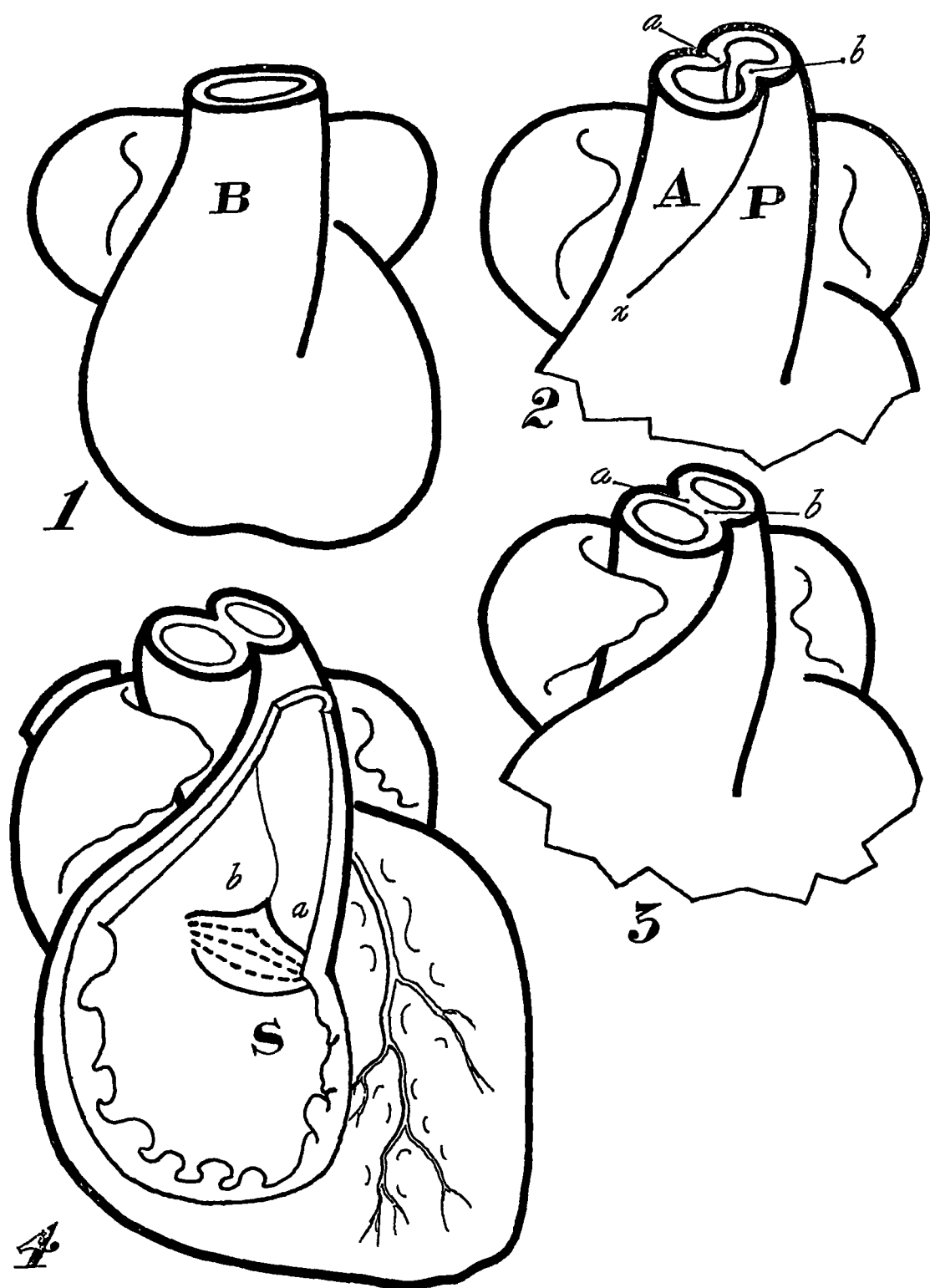


FIG 4 Development of Bulbus Cordis 2-3, a and b—lateral swellings which fuse and form the bulbar septum 4—diagrammatic representation of the closure of interventricular foramen

the museum of the Royal College of Surgeons of England and furnished a large number of the 270 specimens studied and reported by Keith<sup>1</sup> in 1909. Since that time, many worthwhile contributions have appeared in medical literature and among them an exhaustive monograph by Abbott<sup>2</sup> takes rank as a recent comprehensive study of reported cases.

It is the opinion of most observers that congenital defects of the heart represent faulty or arrested development occurring before the eighth week of embryonic life, at which time the heart in miniature is completely formed. In Abbott's study of 850 cases, 17% were associated with malformations of other parts of the body and some with mental deficiencies. Cases of fetal endocarditis occurring in the course of maternal infections are recorded. Rarely are there histories of familial tendencies to heart anomalies. Cunningham<sup>3</sup> suggested that alcoholism and drug taking might be factors in their production, but this and the theories involving maternal impressions and trivial injuries sustained by the mother during pregnancy have been quite generally discarded.

In 1907, Peter Thompson identified and described the development of the bulbus cordis in the human heart. Within its lumen in the 5 mm embryo four longitudinal swellings arise. The two lateral thickenings later fuse, and the later, spiral, clock-wise movement of the bulb and ingrowth of connective tissue eventually divide the aorta from the pulmonary artery, placing the opening of the former over the left ventricle and the latter over the right

While this development is taking place, the interventricular septum begins to grow upward from the base of the ventricular cavity to join the endocardial cushions. The union of these two structures at about the seventh week forms a temporarily incomplete partition between the right and left ventricles and the lower border of the interventricular foramen, which has as its upper boundary the proximal margin of the bulbar septum. The formation of the septum membranaceum which later closes this foramen is said, therefore, to depend upon the proper fusion of the descending bulbar septum with the upper margin of this dividing wall. Keith and Greil were the first to suggest that the malformations which include interventricular defects at the base of the septum in the region of the pars membranaceum represent imperfect closure of the interventricular foramen and are due to an arrest in the development of the bulb. Such defects seldom occur alone, but associated with pulmonary stenosis, dextroposition of the aorta, and right ventricular hypertrophy, constitute a tetralogy described by Fallot as the most common combination of defects found in individuals living beyond the age of childhood. Rokitsansky suggested that the anomalies resulted from a deviation of the bulbar septum with consequent alteration in the size of the great vessels. Others affirm that they are due to the persistence of the reptilian right aorta. Independent defects have been explained as primary arrestments in growth of unknown origin.

Symptoms of congenital heart diseases are usually present from birth,

but occasionally may not be manifest until adolescence or later. The chief diagnostic features are cyanosis, clubbing of fingers and toes, cardiac murmurs, and early hypertrophy.

Congenital cyanosis differs from cyanosis of the later stages of acquired heart disease in that it may exist for many years without any sign of heart failure. With clubbing of the fingers and dyspnea it is one of a triad of symptoms aforesaid known as cyanopathy or morbus coeruleus. It varies according to the character of the defect, from a slight bluish tinge appearing upon exertion to extreme purple discoloration about the cheeks and mucus membranes. Extreme grades are found where there is interference with the circulation to the lungs or where the blood from both ventricles enter the circulation through the aorta. In independent patent foramen ovale it usually is slight or absent until it occurs as a terminal condition.

Associated with cyanosis there may be more or less increase in the number of red cells and the percentage of hemoglobin, and the urine may contain a large amount of albumin.

Dyspnea may be present only after exertion, or associated with other symptoms of heart failure become a prominent symptom of myocardial insufficiency.

The heart is usually considerably enlarged. The left border of dullness may extend well beyond the mid-clavicular line in the 5th or 6th interspaces, and the right border also may extend beyond normal limits. Thrills may or may not be present. In septal defects, a systolic murmur is usually found along the left border of the sternum.

It may sometimes be heard in the subscapular region. Murmurs are variously described according to their volume and character of sound.

Most cases of congenital heart disease die before the end of adolescence. Bacterial endocarditis is the most common cause of death. White and Sprague<sup>1</sup> reported the longest lived case on record. The patient was a noted musician who lived to be sixty years of age and died in coma following an attack of complete hemiplegia, "the heart carrying on a satisfactory circulation to the end."

#### SUMMARY

1. A child of normal mental and otherwise normal physical development, who passed through several acute illnesses and took part in usual childhood activities, lived until past fifteen years of age with a functioning tetralogy of Fallot.

2. Subacute bacterial endocarditis of the pulmonary valve, probably the result of an acute respiratory infection eleven months before, eventually caused occlusion of the narrow pulmonary orifice which was followed by collapse of both lungs and sudden death.

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# Syphilis of the Stomach—A Study of Eight Cases\*

By JOHN B FITTS, M.D., F.A.C.P., Atlanta, Ga

VISCERAL syphilis has become of increasing interest and importance in recent years due to more accurate diagnosis, and to an appreciation of its wider incidence. Lesions of tertiary syphilis manifesting themselves in the cardio-vascular and central nervous systems are being more and more emphasized today. The gastro-intestinal tract is less often affected, perhaps, by the spirocheta pallida than any of the viscera. Gastric symptoms in syphilis may be many and varied, they may be independent and superimposed upon an existing syphilis, or the expression of symptoms of central nervous system lues, as gastric crises, or reflexly from syphilis of other viscera. The cases studied in this series, however, refer to the actual involvement of the stomach by the syphilitic process, so-called gastric syphilis.

Eusterman divides the history of this subject into three periods, namely (1) The post-mortem period extending up to 1905, characterized by the extreme rarity of cases (2) The period of 1905 to 1910, characterized by the clinical classification of cases, and the (3) period from 1910 to the present when the classification of cases were more accurately placed by the Wasserman reaction and the X-ray

The material from which this study is made offers a somewhat different approach than that found in the literature on this subject. The material used is derived from the medical wards of a hospital where the admission of the Southern negro is utilized for teaching purposes. This hospital was opened eight years ago, and to date has had 35,000 admissions. Southern clinicians have long been aware of the tremendous incidence of syphilis among the negro race. Those of us working in the medical ward have been impressed with the large number of cardio-vascular and central nervous system luetics. As the gastro-intestinal tract is less often involved by syphilis, it was thought that it would be of interest to ascertain the incidence of gastric syphilis occurring in this type of clinical material. A routine Wasserman is done on all patients, and of all blood specimens submitted to the laboratory thirty per cent are strongly positive. The actual clinical incidence of syphilis in these patients we believe to be much higher, a 75% incidence would be nearer the truth. In these 35,000 admissions in all services in eight years there have been eight cases of gastric syphilis in the medical wards. In 500 autopsies during the past three years definite demonstrable gastric lues has not been found. Despite the fact of the known

\*From the Department of Medicine, School of Medicine, Emory University

tendency to immunity of the gastro-intestinal tract to syphilis, it would seem that in this type of material it would be encountered more frequently. However, out of the 35,000 admissions in the eight year period we have records of only eight cases of gastric syphilis.

The findings in these cases in brief are as follows —

*Case 1* L M, male, age 32 Chief complaint vomiting p.c. for one year, with weight loss of 54 pounds and history of penile sore. Physical examination, no palpable mass abdomen.

Laboratory data—Blood Wasserman strongly positive Red cells 5,210,000, Whites 6,000

Gastric analysis free HCl 20, total 55

X-ray examination — Stomach shows spasm at pylorus suggestive of ulcer or syphilis

Course—Remained in hospital 9 weeks Antiluetic treatment

Discharged improved X-ray still shows prepyloric defect

*Case 2* W J, male, age 45 Complaint of pain stomach p.c. vomiting and weight loss of 25 pounds

Laboratory data—Blood, strongly positive Wasserman Red cells 4,227,000, Whites 6700

Gastric analysis—free HCl 24, total 59

X-Ray—Stomach narrowed and appearance that of malignancy

Course—Remained in hospital 1 month Antiluetic treatment

Discharged improved X-ray shows improvement in stomach deformity

*Case 3* C H, male, age 63 Complaint pain in stomach, weakness, for 6 months Loss of weight

Gastric analysis—No free HCl

Blood—Wasserman strongly positive Red cells 3,690,000, Whites 9,800 Spinal fluid Wasserman negative No palpable tumor

X-Ray—Infiltrating defect along lesser curvature

Course—After antiluetic treatment discharged from hospital, improved and X-ray shows lessening of stomach deformity

*Case 4* L M, age 32, male Complaint of pain epigastrium and vomiting Weight loss of 54 pounds in 6 months History of penile sore 9 years previously No palpable tumor

Laboratory data—Blood Wasserman, strongly positive Red cells 4,000,000, Whites 5,200

Gastric analysis free HCl 20, total 55

X-Ray—Defect on lesser curvature stomach

Course—After antiluetic treatment, no further pain X-ray shows marked improvement in outline, which has returned to about normal

*Case 5* C M, age 22 Chief complaint pain and vomiting for seven months History of penile sore 3 years ago Loss of 30 pounds in weight

Laboratory data—Gastric analysis—no free HCl

Blood—Wasserman strongly positive Red cells 4,830,000 Whites 14,000

X-ray shows no defect in gastric outline

Course—Hospital 6 weeks and after antiluetic treatment, shows marked improvement and is able to retain food

*Case 6* W N, male, age 20 Chief complaint pain in stomach, vomiting, loss of weight for 7 months History of penile sore No palpable masses in abdomen

Laboratory data—Gastric analysis free HCl 35, total 38

Occult Blood positive Wasserman strongly positive Red cells 3,830,000, Whites 7,300 Blood chemistry normal Spinal fluid negative

X-Ray—Marked spasm stomach and filling defects about pylorus

Course—Hospital 4 weeks Antiluetic treatment Dismissed condition improved

*Case 7* A S, male, age 25 Chief complaint, vomiting, pain, weakness Loss of 30 pounds in weight History of syphilis 3 years previously

Laboratory data—Gastric analysis no free HCl

Blood—Strongly positive Wasserman Red cells 1,900,000 Whites 7,700 Hgb 50% Blood chemistry normal

Stool—Occult blood negative

X-Ray—Stomach negative except for irregular duodenal cap

Course—After three weeks antiluetic treatment, looks and feels better, and Hgb has increased from 50 to 85%

*Case 8* W M, male, age 27 Chief complaint vomiting, inability to retain food for 12 months Penile sore 3 years ago No palpable mass in abdomen

Laboratory data—Gastric analysis, no HCl present Stool positive for occult blood Wasserman strongly positive Hgb 80%, red cells 4,590,000 Whites 9,000

X-Ray—Stomach tubular, hour glass type Pylorus gaping

Course—Hospital 5 weeks Antiluetic treatment Relief of symptoms Gain of 30 pounds in weight Repeated X-rays, no change in gastric deformity Absence of Hcl persists

*Comment* One notes that in this series of cases all are males From the literature it would appear that the sex ratio is two males to one female

The age incidence in this group is greatest between 20 and 30 The history of onset is from 2 months to 18 months All of the series have a clinical history of syphilis All have strongly positive Wasserman reactions All have suggestive symptomatology All show improvement after anti-luetic treatment

*Symptomatology* The chief clinical symptoms are—great weight loss, secondary anemia, epigastric pain and persistent vomiting with the inability to retain food

*Physical Findings.* It is characteristic of gastric syphilis that palpation of the abdomen reveals no masses, although this may occur, of course Epigastric tenderness is elicited. This is diffused and shows no localization

*Laboratory data* The blood usually shows a positive serology, although a negative serology may exist with definite clinical evidence of the disease Low hemoglobin, low red cell count Gastric analysis usually shows an absence of hydrochloric acid, which persists even after treatment. The stools may or may not show occult blood

*Roentgenological Findings* Evidence of infiltration of the gastric wall, obstruction, or of gaping pylorus occurs in this series, and in only one case was the stomach negative roentgenologically. The X-ray signs of gastric syphilis are

(1) A concentric, symmetrical defect of the gastric lumen

(2) The stomach appears high, and the lumen narrowed

(3) If the lesion is antral it appears in a narrowed tubular effect

(4) If the lesion is of the hour glass type, the isthmus of the hour glass is elongated and dumb-bell like

(5) The pylorus may be gaping, or less frequently obstructive

(6) Six hour residues are not found except in the obstructive type

(7) The technical point of differentiation from carcinoma lies in the fact that the syphilitic lesion is symmetrical while the carcinomatous is irregular and asymmetrical Where both lesions are at the pylorus it may be impossible to differentiate

Syphilis may involve the stomach in three ways, namely (1) A diffuse syphilitic gastritis (2) Syphilitic ulcer, (3) Gummatous infiltration

Perhaps the large infiltrating gummatous lesion is the one most frequently diagnosed The consensus of



opinion is that in no sense is peptic ulcer etiologically related to syphilis, although this view is held by Parody. It should be remembered that syphilitics can develop peptic ulcer or carcinoma independent of constitutional syphilis and their treatment responds to non-specific measures. It is said that syphilis of the stomach occurs once to every one hundred other organic lesions such as ulcer or cancer. It is interesting to note that in only one case in the literature have spirochetes been demonstrated in the gastric lesion, that of the case of McNee, and the authenticity of this case has not been accepted by some recent writers.

*Treatment* Antiluetic treatment produces marked improvement, the symptoms abate, weight increases, and the infiltrating gastric lesions regress, although in some cases X-ray shows the structural defects persist. Achylia, which occurs frequently in the disease, also persists after treatment. Achylia in syphilitics has been observed for some time.

It is to be remembered that syphilis may accompany an organic lesion and

that a general improvement under antiluetic treatment may occur, which may be misleading, and valuable time in operating on a malignancy may be lost.

In the management of a gastric hemorrhage of unknown origin, it has been brought out by some observers that the etiology may be syphilitic.

### CONCLUSIONS

(1) Eight cases of gastric syphilis are tabulated occurring in an admission of 35,000 cases in a general teaching hospital.

(2) Comment is made that so few cases have occurred in such a large syphilitic material.

(3) Presenting symptoms in gastric syphilis are—pain, vomiting, loss of weight, Positive blood Wasserman, and characteristic X-ray findings.

(4) The attributing of all gastric symptoms to an existing constitutional syphilis is to be avoided, as they may be entirely independent thereof.

(5) In the investigation of chronic disease of the gastro-intestinal tract syphilis may be the etiologic factor.

# Observations of Heart Action Under Vagus Stimulation\*

By AUDLEY O SANDERS, M D  
*U S V B Diagnostic Center, Palo Alto, California*

FOR some years the view has been held by observers of first rank that the right vagus is commonly more intimately associated with the sino-auricular node and its activities than is the left vagus. It has long been noted that the slowing of the heart as result of stimulation of the right vagus is usually more marked than is the slowing as result of stimulation of the left vagus. It is certainly also a matter of common observation that in any group of normal adults the individuals vary greatly one from another in their responses to vagus stimulations. Accumulated routine records of normal variations should throw suggestive light on the problems of abnormal variations, in that the differences between the normal and the abnormal may often be only those of degree.

With the foregoing thoughts in mind it occurred to the writer that a report of the differences in responses to right and to left vagus stimulations in a series of fifty adult males, with apparently normal hearts, might be of some clinical interest.

This report includes the routine observations of fifty men whose ages

ranged from 30 to 60 years, all being, at the time the observations were made, in fairly good general health. These records are chiefly those of the responses to stimulation of the right vagus and to like stimulation of the left vagus by digital pressure on the respective nerve and its neighboring structures within the corresponding carotid sheath, at the position in the neck where they were most readily accessible, this being near the level of the body of third cervical vertebra.

It should be borne in mind that these responses may not have been entirely due to the vagus stimulations alone, for the associated pressure on the carotid artery certainly did markedly diminish the arterial blood supply to the brain. It was regularly observed that for the period that the pressure on the carotid sheath was continued the radial pulse was notably decreased in volume and that immediately the pressure on the carotid sheath was released the radial pulse regained its former character.

It was something of a surprise to find that in this group the ages of the individuals were of little importance in the classification of their response to vagus stimulations. The younger men were not more responsive to the vagus

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stimulation tests than were the older men. As a matter of fact, the two men who showed the most marked pulse slowing with vagus stimulations were 43 years and 56 years of age respectively. These men were both quite self contained and showed no nervous or neurotic manifestations. Neither of them gave any history of cardiac trouble and neither had any other physical findings suggestive of cardiac abnormality except that one of them had a rather marked sinus tachycardia.

It was also observed that the men who had very definite respiratory sinus arrhythmia were not more apt to show marked pulse slowing from direct digital pressure on the vagi in the neck than were those men whose electrocardiograms gave no suggestion of respiratory sinus arrhythmia.

Of the 50 individuals of this group, five (10%) showed no responses at all in the rate or character of the pulse as

result of digital stimulation either of the right or of the left vagus; forty-four (88%) showed definite slowing of the pulse as result of the digital pressure and one (2%) showed a slightly increased pulse rate, from 54 to 60, with digital pressure, this increase being the same with pressure on the right as on the left vagus.

With fourteen (28%) of the individuals the pulse slowing on stimulation of the left vagus was equal to the slowing on stimulation of the right vagus, with three (6%) the slowing on stimulation of the left vagus was more marked than the slowing on stimulation of the right vagus and with twenty-seven (54%) the pulse slowing was more marked on stimulation of the right than on stimulation of the left vagus. It is of special interest that, of the three individuals who showed more response to stimulation of the left than to stimulation of the right vagus, the

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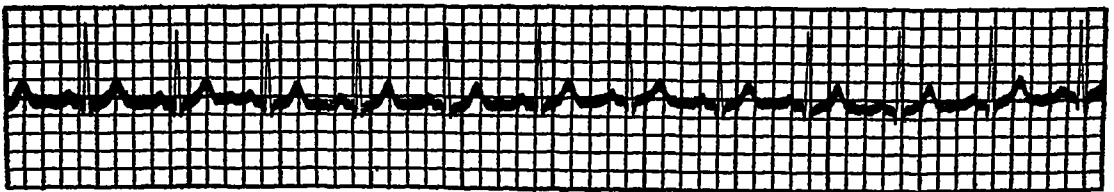


FIGURE 1. LEAD I.

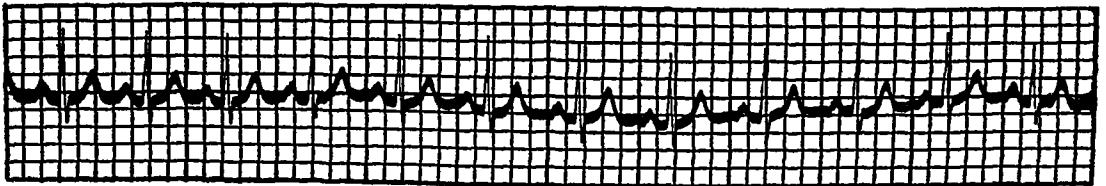


FIGURE 2. LEAD II.

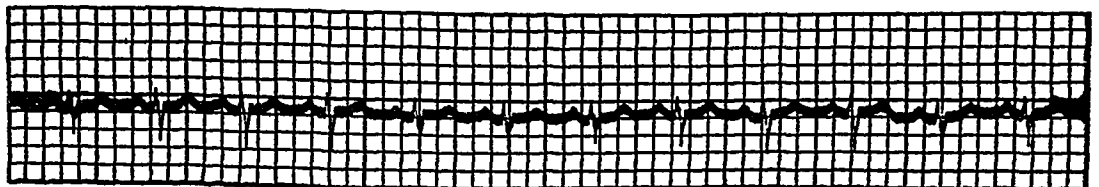


FIGURE 3. LEAD III.

one who showed the most marked response on left vagus stimulation was a man with congenital dextrocardia and apparently complete transposition of thoracic and abdominal viscera

Electrocardiograms are here presented of the one man in this group of fifty who showed the most notable pulse slowing with vagus stimulations. These electrocardiograms are of a practicing physician, 43 years of age, who for a long time has been aware of his marked susceptibility to vagus stimulation. Figures 1, 2 and 3 are records of the 1st, 2nd and 3rd leads taken just before the vagus stimulation experiments were started. It will be observed that there is nothing remarkable in these except that the rate is rather rapid, 120, and that there is a very slight sinus arrhythmia which is of the respiratory type. Figure 4 was taken as the patient breathed very slowly and deeply and the record shows the respiratory sinus arrhythmia

to be slightly more evident. Steady and firm pressure was then made on both eyeballs, but the record is not here reproduced for the reason that no slowing of the pulse rate or other features of interest were shown. Figure 5 is the record as digital pressure was made on the left vagus. It will be observed that with pressure on the left vagus the pulse rate decreased at once from 120 to 75, but that there is otherwise very little change to be noted.

Figure 6 shows the sudden and very marked slowing as digital pressure was made on the right vagus, the period of heart stand-still between beats having been two full seconds. Except for a slight widening of the T, no notable changes in the complexes are observed at first. As the digital pressure was repeated, with only a few moments of intermissions, constantly varying records were produced, some of which are shown in Figures 7, 8 and 9. In Fig-

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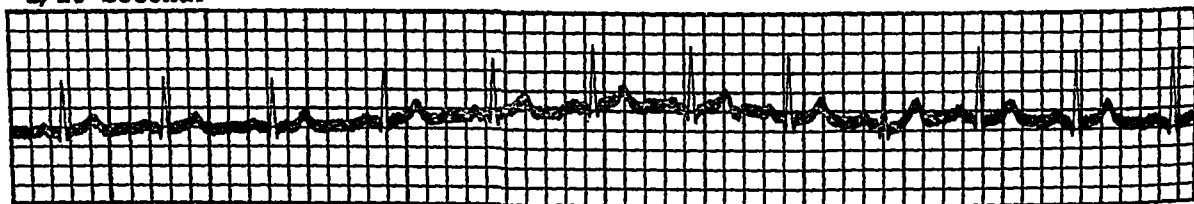


FIGURE 4. LEAD I.

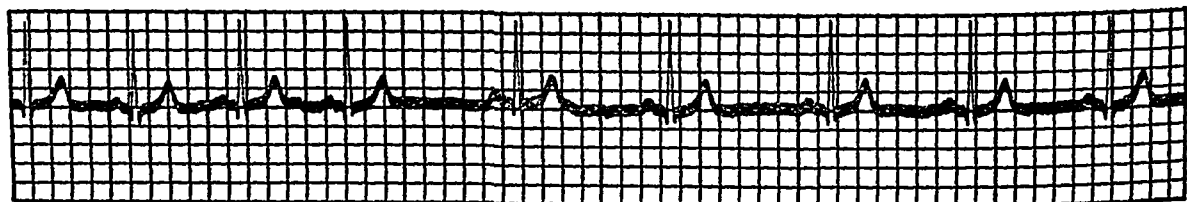


FIGURE 5. LEAD I.

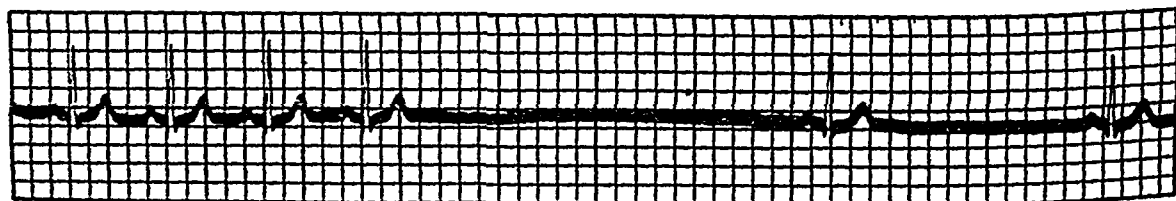


FIGURE 6. LEAD I.

ures 7 and 8 the pacemaker is seen to have shifted to various positions, and in Figure 9 the heart is seen to have stood still for approximately  $3\frac{3}{4}$  seconds, representing the period of 7 regular heart beats. Peculiarly the complexes which immediately followed the long pause are quite normal in character.

#### CAUTION

Due consideration for the comfort and safety of the subject should always be kept in mind. By careful and steady pressure with the ball (not the end) of the thumb unnecessary discomfort can be avoided. The physician who was the subject of the electrocardiograms here reproduced was apparently not at all annoyed by the experiences incident to the making of these records. With such interested and co-operative subjects the examiner may be strongly tempted to multiply and vary the routine tests. Here a serious word of caution should be sounded. *One should not attempt to*

*stimulate both vagi at the same time.* Sir Thomas Lewis states that harm has resulted from such an experiment.\*

#### CONCLUSIONS

1. There are evidently very great variations in the responses of normal individuals to vagus stimulations.

2. It is most difficult to determine just where to draw the line between the normal and the abnormal responses to vagus stimulations.

3. Of the fifty individuals observed twenty-seven showed more slowing of the pulse on stimulation of the right vagus and only three showed more slowing on stimulation of the left vagus, which seems to support the view that the right vagus commonly has more control over the sino-auricular node than has the left vagus.

\*LEWIS, SIR THOMAS. *The Mechanical and Graphic Registration of the Heart Beat*, 3rd Edition, 1925, p. 430.

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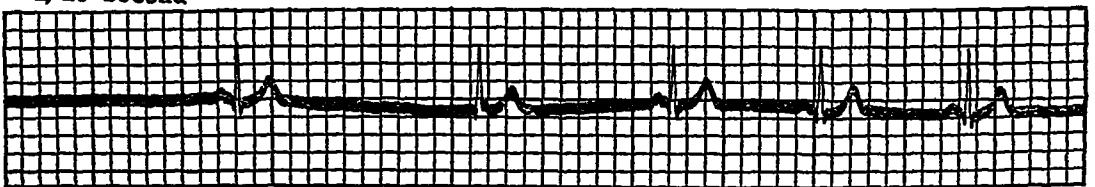


FIGURE 7. LEAD I.

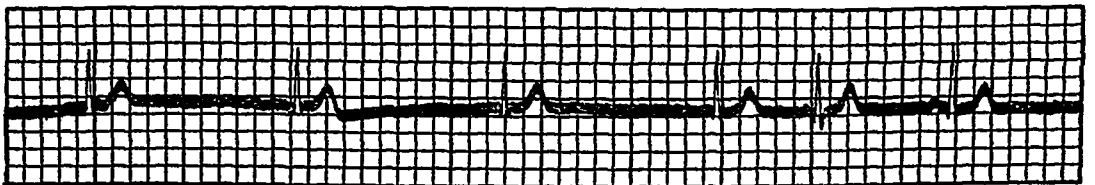


FIGURE 8. LEAD I.

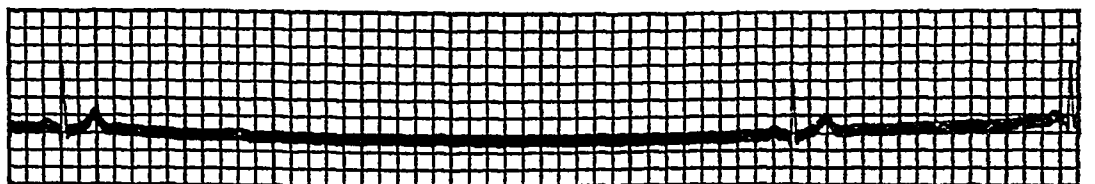


FIGURE 9. LEAD I.

## Editorials

### GALEN

130-1930

This year marks the eighteen-hundredth anniversary of the birth of Galen who in his early thirties won such distinction as a practitioner in Rome that he became known as "Paradoxologus," the wonder-speaker, and "Paradoxopoeus," the wonder-worker. He was born in Pergamus in Mysia. He began the study of medicine at the age of seventeen, and in his twentieth year went to Smyrna in order to study anatomy under Pelops. He visited other Mediterranean schools, and finally went to Alexandria. In the course of his wanderings he studied anatomy under three of the pupils of Quintus, who was himself the pupil of Marinus. The latter had written a complete textbook on anatomy, which has been lost. Of this teacher Galen wrote that everything he described he had "touched with his own hands and seen with his own eyes." About 160 he went to Rome where he remained until 168, when he returned to his native city, but went back to Rome in 170. In Rome he had unparalleled success as a practitioner, curing Eudemus, a celebrated philosopher, and other noted persons, also incidentally, incurring the jealousy of his fellow practitioners. He finally became personal physician to the Roman Emperors from Marcus Aurelius to Septimus Severus. Galen was a born investigator. During his

early days in Rome he held public dissections of animals. He constantly studied, taught, criticized, observed, and investigated. He was one of the most versatile and accomplished writers of his age. It is said that he composed nearly 500 treatises on a great variety of subjects, including logic, ethics, and grammar. Of the works attributed to him, 83 are recognized as genuine, 19 are of doubtful authenticity, 45 are spurious, 19 are fragments, and 15 are notes on the writings of Hippocrates. He rewrote all of ancient medicine in the light of his own experience and observations. It is, however, not always possible to distinguish what was original with Galen, or what was known to the older anatomists. To the modern reader the works of Galen seem unsystematic, repetitious, and often inconsistent. He applied descriptive phrases rather than names to anatomical structures, and this habit makes his writings difficult and tedious. His style was, however, clear and animated. But within this great mass of writing, there is, however, a very complete account of the structure of the animal body. This knowledge was confined, by the circumstances of the times, to the dissection of animals, and this led later to great confusion which was cleared up by Vesalius. Galen was a thoroughly practical anatomist. He not only describes the organs, but gives ample

directions for their dissection and exposition. He appears to have been the first anatomist to attempt to discover the uses of organs by vivisection and experiments on living animals. In this way he determined the position and movements of the living heart. Through a series of experimental observations he demonstrated that section of the optic nerve caused blindness, and that section of the oculomotor nerve destroyed the motion of the eyeballs. Galen's osteology was the most perfect branch of anatomy of the ancients. In the branch of myology he appears to less advantage, though advancing this field of anatomical knowledge to greater perfection than any of his predecessors. His knowledge of the circulatory system was vitiated by the erroneous physiology of the period, yet presents some accurate observations showing his skill in dissection. He worked out a fairly well detailed account of the brain, and recognized seven pairs of cranial nerves. In his account of the thoracic and abdominal organs his descriptions are in general accurate. His description of the reproductive organs is brief and too much confused with physiological dogmas. The anatomical writings of Galen constitute a remarkable era in the history of anatomy. Through his diligence in dissection and accuracy of description, he gave the science a position of importance which it held for many centuries. He attained a position of universal authority in anatomy. He was read, quoted, and copied for thirteen hundred years. During this period his statements were never questioned, or tested by independent observation. His books were trans-

lated into Syriac and Arabic. There were no separate original books on anatomy in Arabic, but the encyclopedic works of Rhazes, Alī Abbas, and Avicenna, in the tenth and eleventh centuries, contain long chapters on anatomical subjects. These all had their origin from Aristotle and Galen. Galen's anatomy we know to have been derived from animal dissections. In the Arabic textbooks his anatomy was applied to man without question, hence during the Middle Ages was accepted as authoritative and final. By the middle of the thirteenth century, the Italian translators had Latinized Aristotle, much of Galen, and the majority of the Arabians. Chaucer's "Doctour of Phisik" knew well his "old Ypocras and Galien." The pre-Vesalian anatomists retained intact the Arabic Galen-traditions. These ruled supreme until Berengario at Bologna in the early sixteenth century first subjected the authority of Galen to critical examination, and denied the so-called middle ventricle of the heart and the multichambered uterus, and openly and frankly declared that he was confused by the discrepancy between some of Galen's descriptions and the actual anatomical findings in human bodies. In 1525 a complete edition of Galen in Latin was issued by the Aldine press. This publication permitted the true evaluation of the ancient knowledge. In the earlier years of his career Vesalius was a follower of Galen, but about 1540, being asked to assist in editing a complete Latin edition of Galen, he became greatly perplexed by the discrepancies between Galen's descriptions and the human body. During this year he happened to find a

bony process, the anapophysis, in a monkey's vertebra, which had been described by Galen, but which he himself could not find in man. The truth flashed upon Vesalius—Galen had written his descriptions from animals, and not from the human body. Thus was the Galenic anatomic tradition of fourteen centuries broken, and the foundation for the modern science of anatomy securely laid. In his theory of medicine and medical practice, Galen was a follower of the Hippocratic doctrine of humors. Thus he developed with great but fatal ingenuity into the theory of normal temperaments and the abnormal distempers. The latter were not diseases but were the occasions of disease. Equal importance attached to dyscrasias or faulty mixtures of the blood. All diseases were produced through the combination of these morbid predispositions with the action of harmful influences from without. On this system he explained all diseases, giving to every phenomenon a name, and having a solution for every problem. In this fine-spun philosophy he departed farthest from scientific principles. He based his use of drugs upon the same theories of hot, cold, moist, and dry, as in the human body; and on the principle of curing by contraries, the use of one or the other was indicated. Galen's theoretical explanations and dogmatic expositions appealed to the indolent mental habits of succeeding ages. His system gained in favor during the middle ages, assuming a position of autocratic influence throughout Europe until the development of modern science in the seventeenth and eighteenth centuries.

Out of Galen arose the greater part of modern European medicine.

### *THE INFLUENCE OF SUPRARENALIN (EPINEPHRIN) ON THE GROWTH OF CARCINOMA AND SARCOMA IN ANIMALS*

Since the isolation by Abel of the active principle of the suprarenal gland in 1897, this substance has been widely used as a vaso-constrictor and hemostatic agent. These properties naturally suggested that the active principle, epinephrin, might have a destructive effect upon certain types of neoplasm. In 1910, Reicher reported that the injection of adrenalin in the neighborhood of rat sarcoma and mouse carcinoma caused a central necrosis and subsequent destruction of these tumors. Uhlenhuth, Haendel, and Steffenhagen found that the local application of adrenalin had very little therapeutic effect on rat sarcoma. On the other hand, Lumsden and Stephens reported that the injection of adrenalin and anti-Jensen rat sarcoma serum into and around the Jensen rat sarcoma caused regression of the tumor and produced active immunity in the animal. At the International Physiological Congress in Boston, in 1929, Sokoloff showed that the intra-tumor injection of a mixture which contained adrenalin, pyrrol blue, and ferric chloride, produced local regression of transplanted tumors in rats and mice. Sugiura and Benedict, about six years ago, carried out an extensive investigation on the effects of epinephrin on transplanted animal tumors. Although they observed regression and apparent destruction of the transplanted tumors



in a large percentage of the transplanted tumors, they were pessimistic as to the application of this hormone in the treatment of human cancer. In the *Journal of Cancer Research*, October, 1930, they report these earlier experiments, and at the same time answer the question as to the possible value of epinephrin in the treatment of malignant neoplasms in the human being. They investigated the toxic action of suprarenalin on the Flexner-Jobling rat carcinoma and the Rous chicken sarcoma in three different ways: namely, 1, injection directly into and around the tumor, 2, injection subcutaneously at a point away from the tumor, and 3, *in vitro*. They found as a result of their work that the development of small tumors in animals is completely inhibited by repeated intramural injections of suprarenalin, while large tumors are seldom beneficially affected by repeated injections. The repeated subcutaneous injection of suprarenalin at a remote point does not affect the growth of rat carcinoma and chicken

sarcoma. *In vitro* experiments showed that the proliferating capacity of the Flexner-Jobling rat carcinoma was partially destroyed by suprarenalin, but the Rous chicken sarcoma was unaffected as respects its growth after implantation. Hence, these investigators conclude that any possible value of suprarenalin (epinephrin) for the treatment of cancer is limited to local application. Recently Coffey and Humber have reported that the injection of an extract of sheep suprarenal cortex produced changes in human cancer tissue. This has led to an extensive advertising of this substance by the public press as a cancer cure. The work quoted above of Sugiura and Benedict shows that there is no scientific foundation for a belief in any specific action of adrenal cortex upon neoplasms, and that any possible change produced in them by the injection of such is wholly of a local destructive nature. A thousand other substances can be found that will produce a similar effect.

## Abstracts

*The Etiology of Erythema Nodosum in Children. Its Relation to Early Tuberculous Infection* By Lloyd B Dickey (Amer Jour. of Med Sc, October, 1930)

Observations of nine cases are reported. Three of these were in boys, aged two and a half, two and a half, and fourteen years respectively. Six occurred in girls, aged three, three and a half, nine, ten, ten, and twelve years respectively. In those cases in which previous tuberculin tests had been done, all were negative except in two cases, although at the time of the appearance of the lesions of erythema nodosum, or shortly after, all tuberculin tests were strongly positive with induration, tenderness, and erythema, which in most cases simulated closely the nodular lesions over the tibiae. In one instance the nodules appeared about twenty-four hours after the introduction of tuberculin into the skin. In only two cases in this series was a history of exposure to tuberculosis elicited despite the fact that all skin tests were positive. The author concludes that erythema nodosum may occur in non-tuberculous individuals or in those infected with the tubercle bacillus. The great majority of cases of erythema nodosum in children are associated with a tuberculous infection, and most of the infections are initial and recent. Most children who have erythema nodosum exhibit marked hypersensitiveness to tuberculin given intracutaneously. There may be associated, in addition to the tuberculosis infection, other conditions which possibly influence the hypersensitiveness to tuberculin. In many cases of erythema nodosum in children epituberculous lesions in the pulmonary parenchyma can be demonstrated by roentgenograms of the chest. In the series reported, none of the individuals observed was known to have a very active tuberculous lesion of the lung. The lesions of erythema nodosum, with epituberculous lesions and the positive skin

tuberculin reactions are similar histologically. As erythema nodosum is usually associated in children with early tuberculous infections, proper treatment for the latter condition gives a favorable prognosis as far as tuberculosis is concerned.

*Gout in a Five Weeks Old Infant. An Important Observation with Reference to the Problem of Gout* By E Mayer von Schopf (Klin Wchnschr, November 15, 1930)

Schopf reports a study on a unique case of gout, the youngest case on record. The literature records as the youngest case previously observed, that of a boy of four years, who had a history of symptoms for two and half years. The present case was that of a male infant five and a half weeks old, whose parents were young and healthy. There were two healthy sisters, one and three years old. The paternal grandfather had had swellings on his hands which disappeared under massage. The great-grandfather had died of dropsy. No other history of hereditary taint could be elicited. There was no history of diabetes, obesity, rheumatic affection, or of stone in the family. The father was a laborer. The living conditions were good. Birth was normal, and the child active and lively. It took the breast readily, but vomited after almost every meal. Its stools were increased and green. In the third week it developed an increasing restlessness, and the mother noticed that hard thickenings appeared upon the back of the hands, and that the fingers were stiff. There was no fever. Because of the vomiting the child was brought to the clinic with the suspicion of a pyloro-spasm. Examination showed no signs of this condition. No pathological findings were discoverable in either thorax or abdomen. Examination of nervous system was negative. The backs

of the hands showed bean-sized tumors of hard consistency on the extensor tendons of the third and fourth fingers. The skin over the tumors was pale, movable, and without signs of reaction, apparently not painful on pressure. The stools were increased, with small amount of mucus. Albumin in urine. Bile pigment not increased. Sediment of urates. Blood Wassermann was negative. The x-ray examination of the hands showed normal bone and joint structure, the tumors gave no shadows. The differential diagnosis was multiple abscesses? Congenital neoplasm with metastases? Tendovaginitis fibrinosa? On the fifth day the child developed signs of bronchopneumonia, with a leucocytosis of 34,000. On the third day new tumors were observed on the left hand and on the foot. Puncture of the latter led to the discharge of a snow-white pultaceous material, which microscopically showed needle-shaped crystals, arranged in bundles, and also amorphous masses. No bacteria were found. Cultures were sterile. Death took place on the night following the sixth day. The autopsy showed marked cachexia, involution of thymus, paravertebral bronchopneumonia of both lungs. Slight catarrhal colitis. The chief pathological diagnosis was gout. Numerous swellings, firm in consistency were found on the back of both hands. The overlying skin showed no reaction, and was pale and movable. The tumors were well circumscribed, and varied in size from a pea to a plum. A chalky pasty material was found in the subcutaneous tissue, in the musculature and on the palmar aponeurosis. The wrist joint and the articulations of the wrist-bones were covered with white masses. The joints of the lower extremities showed no such deposits. Chemical examination showed this material to be made up of urates. Microscopically it consisted chiefly of needle-shaped crystals, with other forms of crystals of uric acid. Both kidneys were enlarged and swollen. Through the capsule the surface showed an appearance as if covered with grits. The capsule was somewhat adherent. The surface was very pale, and strewn with white, slightly elevated granules. The cut section showed medullary

pyramids and cortex to be infiltrated with white granules and stripes of a pultaceous material. In the pelvis a few white crumbling calculi were found. Microscopical examination of the joints and bones of the hands showed an abundant, chiefly amorphous, deposit of urates, with typical needle and columnar crystals. The bone, cartilage, periosteum, and synovial membrane appeared to be unchanged, and inflammatory reaction was wholly absent. The kidneys showed on microscopic examination marked crystalline deposits. The glomeruli showed no changes. The epithelium of the convoluted tubules was well differentiated, many of the tubules contained hyaline casts. Between the collecting tubules of the medulla there was a proliferation of small spindle-cell fascicular connective tissue. Sudan III gave a light brown color to the epithelium, but there was no marked fatty change. The crystalline deposits for the greater part lay between the tubules of the cortex. They consisted chiefly of fine needles, occasionally columnar-shaped bundles, with radial arrangement. Many of them had a capsule of spindle cells about them, containing foreign-body giant cells. Occasional leucocytes are found between the crystals. In the medullary portion of the kidney part of the crystalline masses lay free, others were found in the dilated straight tubules. Also needle and bundle-shaped collection of crystals were found without epithelial or connective-tissue capsule. The small arteries and arterioles showed no change. The kidney was interpreted as a gouty contracted kidney, similar to that in the adult gouty patient. The deposits of crystals were of extraordinary extent and degree, and the cortex was especially involved in the process. There was but little lime-salt present. The crystalline deposits were predominantly interstitial, but occurred also within the tubules. There was a diffuse proliferation of the stroma. Severe interstitial changes were associated with the urate deposits. These kidneys were differentiated from those of the uric acid infarct of the newborn, but the fact that the deposits were white and not yellow, and in the latter con-

dition the urates are wholly in the tubules and not in the interstitial tissue. Chemically the crystals in this case were monosodiumurate, instead of ammoniumurate as in uric-acid infarction. Moreover, these youngest gouty kidneys show chronic inflammation and contraction. In conclusion This is the youngest case of gout on record. The intensity and extent of the uric acid deposits are very great. The development of tophi took place in very short time. The histologic appearance of these show no evidence of either primary or secondary inflammation. The bones showed no changes. There is no explanation of the cause of the retention of uric acid and its deposit in the tissues. Exogenous factors are completely ruled out. The constitutional pathologic factor is not prominent. The kidneys are true gouty contracted kidneys with abundant deposits of urates in the interstitial tissues. Tissue necroses were not found.

*Bechterew's Disease* By von Ehrlich (Arbeit u. Gesundh., Berlin, R. Hobling, 1930)

The symptom-complex described by Bechterew, Strümpell, and Pierre-Marie is not a disease entity, but is the sequel of an infectious disease. The symptoms appear in the vertebral column only under certain predisposing conditions. Rheumatism plays the chief rôle. Trauma and gonorrhea alone are not responsible. Skeletal anomalies and bad living conditions are important predisposing factors. Not only are the small joints involved, but also the vertebral bodies, disks, and ligaments. The pain is caused by pressure upon the nerves by over-filled veins, and by inflammatory changes in the nerve sheaths. The affection is of an inflammatory nature, after its healing, changes can develop which pathologically and roentgenologically show the picture of an arthrosis. Without a roentgenologic examination, the diagnosis of Bechterew's disease cannot be made. The treatment is chiefly the use of a supporting corset. Labor should not be too hastily resumed. Gymnastics and massage should be directed. From the standpoint of pathologic anatomy the fully developed symptom-complex can be

designated a spondylarthrosis ankylopoetica. The early stage is one of spondylarthriti infectiosa.

*Endocardial Pockets* By Otto Saphir (Amer. Jour. of Pathology, November, 1930, p. 733)

In two cases of subacute bacterial endocarditis of the aortic and mitral valves with insufficiency of the aortic valve, endocardial pockets with openings toward the aorta were found on the interventricular septum of the left ventricle. The initial lesion which brought about the pocket formation was a circumscribed parietal endocarditis. The continuous regurgitation formed the pockets secondarily. In one case of rheumatic endocarditis of the mitral valve with insufficiency of this valve, endocardial pockets were present in the left auricle. These pockets were open toward the mitral valve. They also were primarily inflammatory in origin and formed secondarily after the insufficiency of the mitral valve had been established. In two cases of syphilitic involvement of the aortic valve with insufficiency of this valve, endocardial pockets open toward the aorta were found. These pockets were caused primarily by the mechanical irritation of the regurgitating blood columns. Two cases of syphilitic involvement of the aortic valve with insufficiency of this valve and marked stenosis of the conus arteriosus sinister, and one case of rheumatic endocarditis of the aortic valve with stenosis of its orifice, showed endocardial pockets in the interventricular surface of the left ventricle. These pockets were open toward the apex of the heart. They were brought about by the mechanical irritation of the systolic blood stream acting as trauma upon the endocardium in the region of the stenosed portions. Diastolic endocardial pockets are evidence in favor of the view of actual regurgitation of blood volume. The nomenclature of "diastolic pockets" referring to those open toward the aorta, and "systolic pockets" referring to those open toward the apex (Krasso) is justified. Endocardial pockets cannot be regarded as manifestations of functional adaptation.

*The Relation Between Cardiac Weakness and Angina Pectoris* By H Kohn (Deut Med Wchschr, September, 1930)

Kohn does not believe that either cardiac weakness or overwork of the heart predisposes to angina pectoris. Cardiac weakness, may, however, develop during or after an attack of angina. He is inclined to believe that spasm of the coronary artery is the etiologic factor in angina pectoris. This view has an important therapeutic application. Those who hold the view that cardiac weakness is the underlying cause endorse the use of cardiac stimulants for this condition. If coronary spasm is the real cause, stimulants, such as digitalis and strophanthin are more harmful than helpful, because they cause stenosis of the coronary arteries and thus aggravate the condition instead of improving it. Therefore, in place of these stimulants, nitrites should be given for their antispasmodic effect. If objection is raised against the nitrites because of their habit-forming effects, papaverine or theophylline may be administered with or without sugar solution. Atropine may also be used for its antispasmodic effect. In cases of total occlusion of the coronary arteries, caffeine and camphor may be administered. After an attack rest in bed is necessary, and digitalis may be given for the cardiac weakness. The recurrent pain that accompanies medication with digitalis may be prevented by the use of an antispasmodic in conjunction with the digitalis.

*Multiple Gummas of Heart in New Born* By John W Williams (Amer Jour of Pathology, Sept, 1930, p 573)

Williams reports the case of a full term negro female infant, aged 3 hours, in whose heart multiple grayish nodules were found. These were firm, well demarcated, and showed a small central area of softening. Microscopically they consisted of shrunken muscle fibers with varying amounts of a mucoid and vacuolated substance separating the muscle fibers. This substance has the appearance of debris and contains bits of striated muscle fiber, lymphocytes, plasma cells, monocytes, and polymorphonuclear leucocytes, giving the impression that muscle tissue which might once have been

present had been dissolved, and its place partially filled with these cells. Other areas of muscle showed considerable fatty change. Around the small arterioles there were infiltrations of plasma cells and lymphocytes. Staining for spirochetes showed the presence of enormous numbers. Microscopic examination of the other organs showed no evidence of syphilitic lesions. The mother's Wassermann was strongly positive. The pathology of these nodular lesions was identical with that described by Warthin under the term "myxogumma". The lesion does not appear to be a true gumma, and the author suggests the use of the terms syphilitic cellulitis and fulminative syphilitic myositis as descriptive of the lesion, since it is characterized by muscle destruction and infiltration with lymphocytes, polymorphonuclear leucocytes, monocytes, and plasma cells.

*Metastasizing "Carcinoid" Tumor of Jejunum* By Istvan Gáspár (Amer Jour of Path, Sept, 1930, u 515)

A case is reported of multiple carcinoid tumors of the jejunum, one of which caused intestinal obstruction, with metastases in the mesentery and liver. Histological examination revealed the picture of typical carcinoid tumors. Serial sections definitely indicate that at least two of the tumors originated in the crypts of Lieberkühn. Positive silver impregnation confirms Masson's contention that the origin of carcinoid tumors is in the Nicholas-Kulchitzky-Masson cells in the glands of Lieberkühn. It is apparent that carcinoid tumors may occasionally assume clinical importance. Metastasizing carcinoids of the small intestine have been described by Ransom, Versé, and Schaffer.

*The Present Status of Streptococcus Biologic Products in the Prevention and Treatment of Scarlet Fever* By M V Veldee (Pub Health Rep, August 8, 1930)

In the Conference of Health Officers and the United States Public Health Service in 1926, it was the general opinion that the intradermal reaction to scarlet-fever streptococcus toxin is a fairly dependable measure

of the susceptibility of the individual tested. The majority of the individuals giving a positive reaction can be effectively immunized by the proper use of scarlet-fever streptococcus toxin. The use of scarlet-fever streptococcus antitoxin, either for passive immunization, or for the treatment of the individual with scarlet-fever, is not yet founded on sufficient clinical data to permit a mature opinion as to the efficacy of this form of treatment. The results of an immense amount of research work have been reported since the 1926 conference, yet there seems to be little reason to alter the opinions just mentioned. Agreement is fairly general that scarlet fever streptococcus toxin has found a definite field of usefulness in the active immunization of persons

susceptible to scarlet fever. However, agreement has not been reached as to the number of injections or the total dose of toxin required for the production of immunity. The time has not yet arrived for the proper evolution of scarlet-fever streptococcus antitoxin in the treatment of scarlet-fever. We are still in need of very closely controlled clinical demonstrations of the therapeutic value of such antiserum. There are certain shortcomings which need correction before the health officer can push the use of these new products in the prophylaxis and treatment of scarlet-fever. In order to attain general acceptance and usage, we must have a product which will require fewer doses and cause less reaction.

## Reviews

*A System of Clinical Medicine Dealing with the Diagnosis, Prognosis, and Treatment of Disease For Students and Practitioners* By THOMAS DIXON SOVILL, M D, London Eighth edition 1019 pages, 167 figures, 4 plates in color William Wood and Company, New York, 1930 Price in cloth, \$10 00

This book approaches disease from the standpoint of symptomatology In this new edition every page of the book has been carefully revised The chapters on Diseases of the Lungs and Liver, and the sections on the Pancreas, Mental Diseases, Urinary Examinations, Clinical Bacteriology, and Serum Therapy, have been completely recast Much of the chapters on Debility and the Nervous System has been rewritten Much new material has been added, and the chapters dealing with the specialties have been revised by the experts who wrote them The writer is not in sympathy with the plan of this book It is too one-sided and narrow in its outlook and method It is woefully deficient in etiology, pathology, and the general natural history of disease One might just as well have a card-catalogue of symptoms and treat his patients accordingly The material has not been brought up-to-date, and much of it is antiquated The plan is bad, no good textbook of medicine can be written by following such Various typographical errors occur, as Tularemia is indexed for p 546 instead of 556 This is a book which the student of medicine is advised not to purchase

*Clio Medica* A Series of Primers on the History of Medicine Edited by E B Krumbhaar, M D, Professor of Pathology, University of Pennsylvania Published by Paul B Hoeber, New York Price in cloth, \$1 50 per volume

This series of small handbooks on the history of medicine aims at presenting in a con-

cise and readable form special phases of the development and evolution of the art and science of medicine The presentation of the history of medicine in one volume of necessity makes of that volume a book so large that its size discourages approach by any reader Further, the chronological method, so universally followed in the comprehensive general histories of medicine, makes a more or less disconnected story of the history of the individual branches of medicine, so that any reader interested in the history of such branches, must hew his way through the mass of general material, only to find after all his labor, a disconnected and incomplete presentation of the subject It is to obviate such difficulties that the plan of issuing a number of small primers concerned with different fields of medicine, presenting the history of such in the form of a connected tale was adopted These books are of coat-pocket size, and can be easily carried about until an opportunity presents itself for reading To the busy physician or student, this feature of this edition should make an especial appeal The presence of a small volume at hand is a great saver of time, which on motor-car or railway train could be easily lost or wasted The subject of medical history, treated in subdivisions in this way, lends itself particularly to such utilization of spare time It is extraordinary how much knowledge of the history of medicine can be acquired in this way, almost casually or incidentally, without one's being aware of any effort expended in the process Such methods have always been utilized and employed by the true student He who seeks culture will find it, and often the exigencies of a too-busy life permit only this method of time-saving study and reading It is a method that we should like to see extended to every member of the profession It would be trite to dilate upon the advantages

of reading good things, but it may be pertinent to call attention to the possibilities of these little volumes in helping one to acquire a cultural knowledge of the history of medicine. And then the extraordinary low price at which this series is offered puts it in the reach of every one, even the hard-up medical student! The latter could afford to buy a volume every other three months or so, until finally his set is complete. And what an opportunity is here offered to one who is looking for an appropriate gift to present to medical man or student. At this season of the year such a hint is timely. The volumes of this series are written by well-known authorities in their respective fields, and each volume aims to tell the story of the evolution of some individualized phase of medicine in a compact, complete, and convincing form. Four volumes of the series have already appeared: 1, *The Beginnings Egypt and Assyria*, by Warren R. Dawson, 2, *Medicine in the British Isles*, by Sir D'Arcy Power, *Anatomy*, by George W. Corner, and *Internal Medicine* by Sir Humphry Rolleston. Those in preparation are *Physiology*, by John Fulton, *Pathology*, by A. S. Warthin, *Ophthalmology*, by Burton Chance, *Italian Medicine*, by Arturo Castiglioni, *Medieval Medicine*, by David Riesman, *Psychiatry*, by Charles W. Burr, and *Pediatrics*, by Isaac A. Abt. Other volumes are promised by editor and publisher, as these are published.

*The Beginnings Egypt and Assyria* By WARREN W. DAWSON, F. R. S. B., Fellow of the Royal Society of Medicine, of the Society of Antiquaries of Scotland, and of the Royal Anthropological Institute of Great Britain and Ireland. 86 pages.

The earliest medical documents in the world have come down to us from Egypt and Assyria. It is logical that a consideration of these should form the starting point of the study of medical history, and that an account of them should precede the volumes dealing with the medical progress of later times and other lands. The physical conditions of the Valley of the Nile have preserved for us the records of the most ancient intellectual activities. The

Egyptian custom of mummifying the dead influenced greatly the growth of medical knowledge, although embalming was a religious rite and not medical, it afforded opportunities for the acquisition of anatomy, and overcame the popular prejudice against the opening of the dead body, so that Greek anatomists were enabled to carry out a systematic dissection in Alexandria and elsewhere in Egypt. Three thousand years before the birth of Christ a definite effort developed on the Banks of the Nile to cope with the problems of life and death. Both embalmer and physician were concerned in devising means of protecting the individual against the supernatural dangers threatening his existence. The magical procedures used in both cases had the same object in view, the giving of life which death and disease threatened. The endeavor to prolong and protect life and to avert extinction was the human motive out of which the science of medicine developed. The embalmer preserved the physical body, the magician infused into it the vital substance hostile to disease and essential to the continuance of existence. The Egyptian customs first made anatomical dissections possible. In this way Egypt led the way to facilities for the advancement of knowledge and research which could not otherwise have existed. Because of this the debt of civilization to Egypt is incalculable.

*Medicine in the British Isles* By SIR D'ARCY POWER, K. B. E., F. R. C. S., Eng., Honorary Librarian at the Royal College of Surgeons of England, Consulting Surgeon, St. Bartholomew's Hospital, London. 84 pages.

The history of medicine in the British Isles is largely a history of its medical corporations, which from early times have exercised an influence for good upon medical education and medical practice because their ethical standard has always been high. There is practically no knowledge about the practice of medicine in the British Isles until some years after the Norman Conquest. Saxon medicine, as far as is known, consisted chiefly of charms and spells with potions and local applications made from various herbs, many of which are still in



common use among the people. No one in Saxon times seems to have devoted himself entirely to medicine as a profession, the doctors were called leeches, and in every village there were persons who were thought to possess a special power, God-given or by inheritance, of curing disease. The earliest records in Scotland and Ireland show that medicine was a hereditary occupation. Medicine became a profession after the Norman Conquest, though there does not seem to have been any systematic teaching until about 1423. Medicine was at this time almost entirely in the hands of the Church, although there were undoubtedly a few lay physicians in the large towns. Little is known about the physicians. For the most part medicine was subordinate to their clerical duties. Surgery was carried on by laymen, of whom there were two classes: surgeons proper, or as they would be called now, consulting surgeons, and members of the Barbers Company, the general practitioners who attended the minor injuries of the people. The consulting surgeons existed only in London where they formed a small corporate body known as "The Fellowship of Surgeons." Their members varied from time to time from six to seventeen. They did not teach, and had no apprentices. In time of war they followed this or that leader, and flourished accordingly. The Guild of Barbers stayed at home, took apprentices and thrived. In 1462 the religious element had disappeared largely and the Guild became a company with exclusive rights and privileges. As early as 1423 an attempt was made to establish a joint college of Medicine and Surgery, but owing to the war on the continent, the surgeons trooped away, and that appeared to be the end of the matter. Throughout the 15th century the physicians remained unincorporated. In 1518 they obtained a charter creating a College of Physicians in London. In 1540 the Barbers Company and the Fellowship of Surgeons were incorporated into a single company called "The United Company or Barbers and Surgeons." This lasted until 1745 when it was dissolved, the barbers separated, and the surgeons continued as the "Surgeons Company" which undertook the

teaching of surgery, but fell into disrepute, and the company was dissolved in 1796. Four years later the College of Surgeons was founded by charter and remains today as "The Royal College of Surgeons." "The Society of Apothecaries" was incorporated in 1617. The incorporation of the profession in Scotland and Ireland followed the same lines as in England. The Royal College of Surgeons in Scotland was incorporated in 1778, the Royal College of Physicians in Edinburgh obtained its charter in 1670. The history of the great English hospitals is given, as is also the history of medical education and nursing. Two chapters on the medical societies and the masters of British medicine close this well-written and interesting condensation of the history of medicine in the British Isles.

*Anatomy*. By GEORGE W. CORNER, M.D., Professor of Anatomy in the University of Rochester. 8 illustrations, 82 pages.

This volume reviews the development and evolution of the science of anatomy in six chapters dealing with the following subjects: Chapter I, The Greeks, Galen and Galenic Tradition, Chapter II, The Middle Ages, III, Modern Anatomy, IV, Histology, Embryology, Neurology, V, Current Trends in Anatomy. The actual recording of anatomical knowledge began in very early times, for the oldest written records of the papyri are compiled from earlier books and repeat a traditional lore which had already been codified, much in the style of a modern compend. The first definite investigation of anatomical questions of which we have record is in the sixth century B.C., when Alcmaeon of Croton is said to have dissected animals, to have discovered the optic nerve and the Eustachian tubes, and recognized the prime importance of the brain. The anatomy of the Hippocratic collection is trivial and theoretical. Aristotle and his school did not directly influence human anatomy. In spite of his errors, however, he started a movement in Athens in the study of mammalian and human anatomy which did not die out. It was in Alexandria that for the first time anatomy was developed into a distinct branch of science. The books of Herophilus and

Erasistratus have disappeared but through Galen we have knowledge of their anatomical discoveries. After these two leaders there seem to have been no important investigations carried on in Alexandria, but the school remained the chief center of anatomical teaching for nearly 500 years. Galen advised his pupils to go there for study. Galen revived the spirit of investigative anatomy. Of his preserved work there is enough anatomy to make a volume half as large as Gray's "Anatomy." He described the skeleton very well, and was especially interested in the muscles. After him there was no independent investigation of the medical sciences in the whole Roman Empire. Galen's writing became the universal authority, and were read, quoted, and copied, as supreme, for thirteen hundred years, never questioned, and scarcely even tested by fresh observation. By the Arabian school which followed, Galen's anatomy was applied to man without a question, and was accepted as authoritative and final. During the Dark Ages, Anatomy seems to have disappeared completely. Not until the 13th century was dissection revived, and the way paved for the great anatomical advances of the next four centuries. Mondino was the first teacher known to have taught anatomy from the human cadaver in Europe. At those early human dissections there was no thought of independent critical investigation, the business of the professor was of course simply to verify and illustrate the Galenic lore. Berengario was the first independent investigation of modern times, and his two text books were the first to contain pictures systematically illustrating the text. Through three hundred years of slow development, anatomy had been gradually progressing in both knowledge and technique. It remained for Vesalius to take up the torch lighted by these pre-Vesalian anatomists and to raise anatomy to the position of a pure science. The publication of his "Fabrica corporis humani" marked the death of tradition and authority and the birth of intellectual freedom. The foundation stones of modern anatomical observation and investigation were thus securely placed, and with-

in a generation there were anatomists all over Europe who had learned from Vesalius to dissect and analyze the human body for themselves. Then followed the full fruition of the Age of Anatomy during the 17th century, with the great names of Harvey, and other masters who have left their marks upon the terminology of anatomical science. The story of modern anatomy now follows, with the development of histology, embryology, and neurology, told in a concentrated but interesting form. Now when almost everything has been seen that can be discovered in the cadaver with knife and microscope, the anatomist has received new instruments and new methods of investigation. The older static anatomy is moving toward a functional viewpoint. The dissecting room will always be the starting point of the anatomist's work, but the problems of human structure demand for their solution the utilization of all the resources of science.

*Internal Medicine* By SIR HUMPHRY ROLLESTON, Bart., G.C.V.O., K.C.B., M.D., Hon. D.Sc., D.C.L., LL.D., Regius Professor of Physic in the University of Cambridge, England. 92 pages.

The long story of the development of internal medicine is detailed through the centuries by Rolleston in the following chapters: I, Ancient Medicine, II, Greek Medicine, III, Greek Medicine in Rome, IV, Links between Greek and Modern Medicine, V, the Renaissance and the Seventeenth Century, VI, The Nineteenth Century. This is the least satisfactory of the four volumes published to date. Much of it consists only of a catalogue of names and dates. It is too conventionally treated to hold the interest of the reader. It seems to the writer that in a medical primer of this kind, it is much better to consider the evolution of the subject from the philosophic side rather than attempt a recital of all the individuals concerned in that evolution. Rolleston's book lacks interest and readability, because he has followed the conventional medical history treatment of his theme. It is only a condensed manual of medical history, and lacks the interest of individual literary flavor. Moreover, his choice of American internists for mention

in his book strikes one as very peculiar, and inadequate. Better to have left out all mention of American medicine than to represent it by the poor choice given. It may be urged in excuse of the fact that this book falls so far behind the other three in its performance, that the problem of showing a spiritual or intellectual development of Internal Medicine is perhaps a larger undertaking than in the case of the others.

In conclusion, it may be said that the *Clio Medica* represents an undertaking well conceived and planned, and of great value to medical students and physicians who have cultural bents. In these little books they will find a maximum of intellectual food at a minimum cost and trouble. They can be recommended most highly for the purposes for which they are intended.

# College News Notes

## THE FORTHCOMING CLINICAL SESSION IN BALTIMORE

The Fifteenth Annual Clinical Session of the American College of Physicians will convene in the City of Baltimore during the week of March 23, 1931. The privilege of meeting in this city was made possible through the cordial invitation of the Johns Hopkins University School of Medicine, the University of Maryland School of Medicine, the Medical and Chirurgical Faculty of the State of Maryland, the Baltimore City Medical Society, and the further cooperative interest manifested by the various Baltimore hospitals and civic societies. It is to be hoped that this meeting will at least equal in excellence those which have been produced in recent years in other cities, and it is the belief that all who will attend this meeting will find ample in the way of clinical, laboratory, research and historical interest, well to repay them for the time spent in making the journey.

Local conditions, as well as medical and hospital facilities, greatly affect and alter the construction of programs, and at this writing the actual titles of papers and clinics to be presented, by whom, when and where, are far from being in a completed and final state. Moreover, it is possible that for reasons, both of economy and others, the former precedent of issuing a preliminary program may not be lived up to, though this also is not final. In any event, the final draft of the program of the Baltimore Session will be in the hands of each member in ample time for him to peruse it carefully and make his selections well in advance of the actual time of the meeting. Nevertheless, it has seemed wise to issue a preliminary statement about the meeting in the form of a printed article, outlining thus nearly four months in advance the general scope and construction of the Clinical Week.

At the risk of repetition, the following points with reference to the meeting will bear repetition.

(1) *Time and Place.* March 23-27, 1931, in Baltimore, Maryland.

(2) *Hotel Headquarters* will be at the Lord Baltimore Hotel, and it is important at this point to emphasize the wisdom of making early hotel reservations, whether they be at Hotel Headquarters or at some other of the hotels listed at the end of this article.

(3) *General Headquarters*, at which the registration of members, commercial exhibits and all General Sessions will be held, will be the Alcazar, situated at the corner of Cathedral and Madison Streets, Baltimore, unfortunately, is not yet the proud possessor of a convention hall or auditorium at all adequate to its needs, nor comparable to the buildings of this sort found in cities of smaller population. Nonetheless, it is felt that the Alcazar will meet all of the requirements of the College meetings, and all of the meetings, exhibits, registration offices, etc., are located on the same floor, and in easy access to one another.

The skeleton outline of the entire Clinical Week is given in the diagram below, and certain points require particular emphasis.

(1) Those who are planning to attend the Clinical Session should arrange to reach Baltimore either Sunday evening, March 22, or Monday morning, March 23, since the morning of March 23 is left entirely open, thereby giving members and guests ample opportunity to get settled in their hotel quarters, register at the official registration office, and secure therefrom their cards for the various clinics and lectures, for which they have previously signed up, as has been the custom in the past. Not only are these details important, but it is equally to be stressed that a full attendance at the first

FIFTEENTH ANNUAL CLINICAL SESSION  
BALTIMORE, MARYLAND, 1931

Time	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday
A M	March 23	March 24	March 25	March 26	March 27	March 28
9 00 to 12 30	Morning free Registra- tion Exhibits, etc	3rd <i>General Session</i>	5th <i>General Session</i>	6th <i>General Session</i> General Business Meeting	7th <i>General Session</i>	Entire Day in Washington, D C Clinics, Inspection Tours, etc Under Auspices of Medical Departments of Army, Navy, U S Public Health Service, and Georgetown University  — Full details not yet ready
12 30 to 2 00 P M	Lunch					
2 00 to 5 00 P M	1st <i>General Session</i>	1st <i>Clinical Session</i>	2nd <i>Clinical Session</i>	3rd <i>Clinical Session</i>	4th <i>Clinical Session</i>	
5 00 to 8 00	Dinner					
8 15 to 10 30	2nd <i>General Session</i>	4th <i>General Session</i>	Convoca- tion and Reception to New Members	Annual Banquet	FREE	

General Session, to be held Monday afternoon, is not only desirable but is a courteous acknowledgment to the hosts of the entire meeting. It is the sincere hope of the Program Committee that the hall will be filled when the meeting is called to order sharply at 2 o'clock on the date above mentioned.

(2) It is to be noted that the Convocation this year will be held earlier than has been the custom in the past. Further reference to this will be made in a subsequent paragraph.

(3) It is to be noted that the Clinical Sessions of the meeting will occur in the afternoon, rather than in the morning. This plan has been adopted particularly for the reason that it interferes much less with the teaching of medical students at the Johns Hopkins Medical School and University of Maryland. It will be remembered that this same plan was followed at the meeting in New Orleans, with apparently just as great

success as when the sessions were reversed.

(4) The Annual Banquet will be held on Thursday evening, March 26, presumably at the Lord Baltimore Hotel, and to this, as in times past, ladies are cordially invited.

(5) After the Clinical Sessions have been finished on Friday, March 27, there will be held a Post-Clinical Session Day in Washington, D C, for all those who care to attend what promises to be an extremely interesting and valuable meeting there.

#### GENERAL SESSIONS

At the last meeting of the Board of Regents that was held during the Minneapolis Session, it was decided that the President of the College would be held responsible for the programs of the General Sessions, of which there are seven in all. Following the Minneapolis meeting, the Executive Secretary of the College, Mr Loveland, sent out a questionnaire to all of the Fellows and

Associates of the College, asking for ideas and suggestions for the improvement or alteration of subsequent programs. Many replies of value were received, and the answers analyzed, and an attempt has been made by your President to embody as many of the suggestions submitted as possible in the construction of the General Sessions Program. The main changes that he has attempted to make may be briefly summarized, as follows:

(1) The number of papers in the General Sessions will be fewer than has hitherto been the case—probably never in excess of eight papers, of a maximum of twenty minutes each, in any of the morning sessions, which will run from 9 until 12:30.

(2) The morning sessions will be broken mid-way by an intermission of thirty minutes, which will provide not merely a period of relaxation for the audience but will afford an opportunity for every member of the College to make a careful inspection of all of the exhibits. The importance of this cannot be over-emphasized, for it should be pointed out that the exhibits go a long way toward defraying the expenses of the Annual Clinical Session itself, and, moreover, the exhibits offered are invariably worthwhile, from the standpoint of the internist. It has been none too easy a task to assemble as many exhibits as Mr. Loveland has been successful in securing, partly for the reason that exhibitors are aware of the fact that the members of the College will probably be away from the exhibition hall at least half of each day of the Session. It is, therefore, only fair to urge that interest in the exhibits be intensely manifested at all possible times, but particularly during these intermissions which have been provided for just this purpose.

It will perhaps be of interest to know the general method that has been employed in attempting to provide interesting General Sessions. In the first place, the programs of the preceding three meetings were all carefully analyzed, in terms of subjects covered and of individual presenting essays. This analysis revealed several important and interesting facts, particularly, that in the last two years certain subjects had been, if anything, over-handled—as, for instance, ar-

ticles on tuberculosis and hypertension, and, second, the fact that the same individual had presented papers on two and sometimes on three succeeding programs. It was thought wise, therefore, to endeavor to provide a series of articles which dealt as much as possible with new subjects; and, furthermore, it was decided that an individual who had appeared twice within the last preceding three years would not be invited to present a paper at this particular Session. This plan seemed manifestly fair to all to whom the problem was presented.

In the attempt to secure the greatest possible number of submitted titles, the following general method has been employed:

(1) Personal letters have been sent to a great many individuals, whether members of the College or not, throughout the entire United States and Canada.

(2) A letter was sent to the Governor of every state and territory, asking that he in turn submit the names of all Fellows, or of individuals not members of the College, in his State, who, in his opinion, might have material interesting and worthy of presentation before the College, and to every such person a letter was subsequently sent, requesting that the individual in question submit a title or titles of papers which he might care to present. It was clearly pointed out at the time that all of these letters were sent, that the mere submission of a title or titles in no way obligated the Program Committee to accept them.

The result of this extensive correspondence with men all over the country has been the submission of a great many papers, doubtless of both worth and practical interest. At this writing only a few have been finally accepted, and the final selection will be deferred as late as possible, in order that the Program Committee will have the greatest possible amount of material to select from, in its endeavor to secure new subjects, new authors and wide geographical representation. The total number of papers that can be accepted will be between forty-five and fifty, at the most, and it must be apparent that the responsibility for the final selection is no easy one, nor will final selection be the result of personal ideas and opinions, by any means. The hope is expressed that

those who have shown their willingness to read papers will clearly understand, and entertain no hard feelings, if it is found wise to reject their proposed addresses

The number of possible symposia of great interest is very large. Under consideration at the present time are symposia on blood diseases, oxygen therapy, diseases of the liver, recent advances in endocrinology with particular reference to the newer work on supra-renal extracts, myocarditis, and several others which it is not necessary to mention. The greatest difficulty is to know which of the many equally valuable and interesting ones to accept, obviously, the individual tastes of everyone cannot be met.

#### CLINICAL SESSIONS

To Doctor Maurice C. Pincoffs, Professor of Medicine at the University of Maryland, was delegated the task of arranging for all of the Clinical Sessions. Baltimore has but two medical institutions of learning, namely, Johns Hopkins and the University of Maryland itself. Scattered throughout the city are many modern and excellently run hospitals, in which, however, little if any active teaching is done, at least in conjunction with either of the two Medical Schools. Obviously, the focus of greatest attraction will be the various departments at the Johns Hopkins Hospital and Medical School, and it should be stated at this time that the Heads of all of the Departments of this institution have expressed and are showing an enthusiastic interest in the construction of a program which will open all of the facilities of this enormous plant to the visiting members of the College. The active organization and work, in so far as it concerns the Johns Hopkins Hospital, is under the able administration of Doctor Alan M. Chesney, Dean of the Medical School, and a committee appointed by him. A similar committee, acting under Doctor Pincoffs, will supervise the Clinical Programs to be held at the University of Maryland and its affiliated Hospital. In addition, clinics, ward walks, laboratory demonstrations and the like will be held in many of the non-teaching hospitals of the city, such as the Union Memorial Hospital, Saint Agnes Hospital, at which Doctor Joseph C. Bloodgood does

so much of his work, the Municipal Hospitals, and several of the more private institutions, such as the Howard A. Kelly Hospital, noted particularly for its radium activities, and the Sheppard and Enoch Pratt Hospital, which is one of the most modern dealing with psychiatric problems. This does not by any means exhaust the list.

It has been customary in former meetings to have a certain number of clinics given by distinguished out-of-town clinicians, either Fellows of the College or invited guests, and this custom will be followed again this year, in all likelihood.

It should be further noted that the program, in so far as it concerns Johns Hopkins, will include both the pre-clinical as well as the clinical facilities. The work of the Harriet Lane Home in Pediatrics, the Wilmer Institute for Diseases of the Eye, the Phipps Psychiatric Institute, headed by Doctor Adolf Meyer, and, moreover, the surgical facilities of the Hospital are already being marshalled for the presentation of such border-line problems as are of equal interest to surgeons and internists alike. The Johns Hopkins School of Hygiene and Public Health, with Doctor William H. Howell as its Director, will provide its own program of subjects and demonstrations of interest particularly to Public Health workers and those deeply interested in all lines of Preventive Medicine. Last, but by no means least, the new William H. Welch Department of Medical History will offer a program unique in the annals of the College. As above stated, final details as to topics, clinicians giving them, etc., have not yet been worked out in any of the hospitals, but from the above it can readily enough be seen that plenty can and will be provided to suit the tastes and interests of everyone.

#### CONVOCATION

The Annual Convocation of the College, for the induction of new members, as Masters or Fellows, will be held on Wednesday evening, March 25, at a time and place subsequently to be announced. It is felt that this is, or at least should be, the most formal gathering which the College holds during its Clinical Session, and it is, therefore, earnestly urged that all members and those

to be inducted will appear in evening dress on this occasion, at which time the annual Presidential Address is to be given. Following the Convocation, it is hoped that an appropriate reception to the new members can be held, affording them a chance to meet and know not only the Officers of the College, but also to mingle with those who have been members for varying periods of time. Just how this can best be worked out is still under consideration, but, again, it is hoped that this meeting will be fully attended.

#### ANNUAL BANQUET

As previously stated, this will be held, in all likelihood, at the Lord Baltimore Hotel on the evening of March 26, and at it all members, their wives and guests are urged to be present. The function of such a banquet, it would seem, should be not only a pleasant evening of social intercourse, but it should also provide a message of educational importance to all assembled, and with this in mind, it is now thought that the banquet will be addressed by probably a single speaker of some national or international fame and importance, rather than having the customary after-dinner speeches made by a number of individuals.

#### BUSINESS MEETING

The last half or three-quarters of an hour on the morning of March 26 will be set aside for the holding of the Annual Business Meeting of the College, at which all Fellows and Masters are earnestly urged to be present, so that they may hear in person reports as to the administration and financial status of the College. At this meeting the Nominating Committee, appointed by the President one month after the last General Session, will hand in its nominations for officers, Regents and Governors for the ensuing year, and, finally, on this occasion the incoming President, Doctor S. Marx White, of Minneapolis, will be inducted into office. It is fitting and proper that his induction be marked by a full attendance.

#### LADIES ENTERTAINMENT COMMITTEE

It is hoped and presumed that the Baltimore Session will be graced by the presence of many of the wives of the attending members of the College. Baltimore has long

been famed for its hospitality, and it is an assured fact that an interested and hospitable Ladies Entertainment Committee will see to it that all visiting ladies are interestingly occupied during their stay in Baltimore. Like many other committees, the final plans have not yet been drafted, but no doubt need be entertained as to their fitness and pleasure.

#### POST-SESSION WASHINGTON DAY

It was felt that a great many of the members, particularly those coming from some distance, would not wish to return without paying a visit to the National Capital, particularly if some of the unusual medical facilities of that city could be assembled for their interest and instruction. With this in mind, the matter was taken up with Doctor William Gerry Morgan, President of the American Medical Association and Governor of the American College of Physicians for the District, and through his influence a luncheon was recently held in Washington, at which a number of men of national importance were present, including Surgeon General Ireland, of the Army, Doctor Hugh S. Cummings, Surgeon General of the United States Public Health Service, Doctor C. M. Griffith, Medical Director of the United States Veterans Bureau, Doctor W. A. White, Superintendent of Saint Elizabeth's Hospital, a representative from the United States Naval Medical School, and others, including the President of the Medical Society of the District of Columbia. These men enthusiastically offered their heartiest cooperation in the preparation of a memorable Washington Day, and the number of interesting possibilities was so great that it seemed wise, almost, to change the entire meeting from Baltimore to Washington itself. The facilities of Saint Elizabeth's Hospital and its unusual opportunities of psychiatric study, the Library of the Surgeon General, Army Medical Center, Army Medical School, Walter Reed Hospital, the Smithsonian Museum, the Institute of Public Health, will all be available in a plan which yet remains to be worked out, and this, in turn, will depend largely upon the number of members who express their desire and intention to attend the Washington Meeting.



Such, in schematic form, is the general lay-out for the forthcoming meeting. It is hoped that the lack of specific details will at this time incite rather than dampen further interest in the meeting itself. At least

it can be truthfully stated that Baltimore's welcome will be a wholehearted and unstinting one, and it is believed that all who come will leave repaid.

#### LIST OF BALTIMORE HOTELS

The LORD BALTIMORE HOTEL will be the headquarters hotel for Officers, Regents and Governors, and so far as facilities permit, will accommodate other members and guests of the College. Reservations that the LORD BALTIMORE HOTEL cannot fill, will be referred immediately to some other hotel conveniently located. Those who plan to attend the Baltimore Clinical Session should apply directly for reservations to the hotel of their choice.

(All Prices are for Rates per Day, European Plan)

#### LORD BALTIMORE, Baltimore and Hanover (Headquarters)

Single room with bath	\$3 50 to \$ 6 50
Double room with bath	5 50 to 10 00

#### ALTAMONT, Eutaw Place and Lanvale St

Single room without bath	2 50
Single room with bath	3 00 to 3 50
Double room without bath	4 00
Double room with bath	5 00 to 6 00

#### ARUNDEL, Charles St and Mt Royal

Single room without bath	2 00 to 2 50
Single room with bath	2 50 to 3 50
Double room without bath	3 00 to 3 50
Double room with bath	5 00 to 6 00

#### BELVEDERE, Charles and Chase Sts

Single room with bath	5 00 to 6 00
Double room with bath	7 00 to 12 00

#### EMERSON, Baltimore and Calvert Sts

Single room without bath	2 50
Single room with bath	3 00 to
Double room without bath	4 00
Double room with bath	4 50 to

#### KERNAN, Franklin and Howard Sts

Single room without bath	2 00 to 3 00
Single room with bath	2 50 to 3 50
Double room without bath	3 00 to 4 00
Double room with bath	4 00 to 6 00

#### MT ROYAL, Mt Royal Ave and Calvert

Single room without bath	2 00 to 2 50
Single room with bath	3 00 to 3 50
Double room without bath	4 00 to 4 50
Double room with bath	5 00 to 6 00

#### NEW HOWARD, Howard St and Baltimore

Single room without bath	2 50 to 3 00
Single room with bath	3 00 to 3 50
Double room without bath	4 00 to 5 00
Double room with bath	5 00 to 6 00

**RENNERT, Saratoga and Liberty Sts.**

Single room without bath ..	2 50 to	3 00
Single room with bath	3 00 to	5 00
Double room without bath	4 00 to	6 00
Double room with bath	5 00 to	8 00

**SOUTHERN, Light and Redwood**

Single room with bath	3 00 to	6 00
Double room with bath	5 00 to	8 00

**STAFFORD, Charles and Madison Sts**

Single room without bath	2 50 to	3 00
Single room with bath	4 00 to	5 00
Double room without bath	4 00 to	5 00
Double room with bath	6 00 to	8 00

**BOARD OF REGENTS MEETING**

LOUISVILLE, Ky

NOVEMBER 11, 1930

The Board of Regents of the American College of Physicians met at Louisville, Ky, November 11, on the occasion of the twenty-fourth annual meeting of the Southern Medical Association. President Sydney R. Miller, Doctors F. M. Pottenger, John A. Lichty, S. Marx White, Clement R. Jones, George Morris Piersol, James H. Means, James S. McLester, David P. Barr, Maurice C. Pincoffs, Walter L. Bierring, George E. Brown, John H. Musser, W. Blair Stewart and Mr. E. R. Loveland, Executive Secretary, were present.

The Committee on Credentials for Fellowship, consisting of President Miller, Dr. George Morris Piersol, Chairman, Dr. John A. Lichty, Dr. S. Marx White and Dr. James S. McLester, met on the previous day, November 10, to complete the investigation of 178 candidates. Of this number, the following list was elected by the Board of Regents. In this list is indicated the proposer's name under one, the seconder's name under two, and the endorser's name under three.

**ARIZONA***Phoenix*

Fred G. Holmes

- 1 Allen K. Krause
- 2 James Alex Miller
- 3 W. Warner Watkins

Earle Wood Phillips

- 1 Samuel Watson
- 2 Francis M. Pottenger
- 3 W. Warner Watkins

*Tucson*

Stirley Casper Davis

- 1 Samuel Watson
- 2 Russell J. Callander
- 3 W. Warner Watkins

**ARKANSAS***Hot Springs National Park*

Harley J. Hallett (M.C., U.S.A.)

- 1 R. D. Harden
- 2 George R. Callender
- 3 M. W. Ireland

**CALIFORNIA***Colfax*

Charles Joseph Durand

- 1 Robert A. Peers
- 2 Charles C. Browning
- 3 Egerton Crispin

*Los Angeles*

Harry Welrose Coffin

- 1 Charles C. Browning
- 2 Carl R. Howson
- 3 Egerton Crispin

Madison J. Keeney

- 1 Thomas J. Orbison
- 2 John V. Barrow
- 3 E. J. G. Beardsley

John Mark Lacey

- 1 Charles C. Browning
- 2 Carl R. Howson
- 3 Egerton Crispin

*Palo Alto*

Percival G. Lasché (U.S.V.B.)

- 1 Hugo Mella
- 2 Winthrop Adams
- 3 Philip B. Matz

*Riverside*

- Paul Edward Simonds  
 1 Charles C Browning  
 2 Carl R. Howson  
 3 Egerton Crispin

*San Diego*

- William Hulbert Barrow  
 1 Robert Pollock  
 2 Wm Fitch Cheney  
 3 Egerton Crispin  
 Addison Eugene Elliott  
 1 Lyell C Kinney  
 2 James F Churchill  
 3 Egerton Crispin

*San Francisco*

- William Charles Munly (M C, U S A)  
 1 P M Ashburn  
 2 R. D Harden  
 3 M W Ireland  
 Philip Hale Pierson  
 1 Francis M Pottenger  
 2 Wm J Kerr  
 3 Hans Lisser

*San Pedro*

- Forrest Martin Harrison (M C, U S N)  
 1 P F Dickens  
 2 E E Smith  
 3 C E Riggs

*Woodland*

- Delos Schuyler Pulford  
 1 F F Gundrum  
 2 Robert A Peers  
 3 Egerton Crispin

## COLORADO

*Denver*

- John Thomas Aydelotte (M C, U S A)  
 1 C J Gentzkow  
 2 H C Coburn, Jr  
 3 M W Ireland

## CONNECTICUT

*Bristol*

- Ralph Augustus Richardson  
 1 C Brewster Brainard  
 2 Orin R. Witter  
 3 Henry F Stoll

*Hartford*

- Augustus Roi Felty  
 1 George Blumer  
 2 Orin R Witter  
 3 Henry F Stoll

## James Elder Hutchison

1. Orin R Witter  
 2 C Brewster Brainard  
 3 Henry F Stoll

## Isaac William Kingsbury

1. George Blumer  
 2 Orin R Witter  
 3 Henry F Stoll

## G. Gardiner Russell

1. Orin R Witter  
 2 C Brewster Brainard  
 3 Henry F Stoll

*Meriden*

## Cole B Gibson

- 1 Thomas P Murdock  
 2 C Brewster Brainard  
 3 Henry F Stoll

*New Haven*

## Francis Gilman Blake

- 1 George Blumer  
 2 Orin R Witter  
 3 Henry F Stoll

*Norwich*

## Hugh Baird Campbell

- 1 Orin R Witter  
 2 C Brewster Brainard  
 3 Henry F Stoll

*Shelton*

## Edward James Lynch

- 1 Thomas P Murdock  
 2. Daniel P Griffin  
 3 Henry F Stoll

## DELAWARE

*Wilmington*

## Bartholomew M Allen

- 1 E J G Beardsley  
 2 Olin S Allen  
 3 George Morris Piersol

## William Henry Kraemer

- 1 Henry K Mohler  
 2 Elmer H Funk  
 3 E J G Beardsley

## DISTRICT OF COLUMBIA

*Washington*

## James Earle Ash (M C, U S A)

- 1 George R Callender  
 2 R D Harden  
 3 M W Ireland

George Franklin Aycock (M C., U S A.)

- 1 Ernest R Gentry
- 2 George R Callender
- 3 M W Ireland

Arden Freer (M C, U S A.)

1. Ernest R Gentry
- 2 George R Callender
- 3 M W Ireland

Joseph Burton Glenn

- 1 William Earl Clark
- 2 William Cabell Moore
- 3 Wm Gerry Morgan

Charles Clark Hillman (M C, U S A.)

- 1 Ernest R Gentry
- 2 George R Callender
- 3 M W Ireland

James Alexander Lyon

- 1 Edgar P Copeland
- 2 Thomas S Læe
- 3 Wm Gerry Morgan

Paul Edgar McNabb (M C, U S A )

- 1 Charles F Craig
- 2 P M Ashburn
- 3 M W Ireland

John William Meehan (M C, U S A )

- 1 Charles F Craig
- 2 P M Ashburn
- 3 M W Ireland

Charles R Mueller (M C, U S A )

- 1 Ernest R Gentry
- 2 George R Callender
- 3 M W Ireland

Edward Thomas B Weidner (M C, U S A )

- 1 W. Lee Hart
- 2 George R Callender
- 3 M W Ireland

#### FLORIDA

*Jacksonville*

Louie Limbaugh

- 1 R H McGinnis
- 2 Julius Friedenwald
- 3 Maurice C Pincoffs

*Miami Beach*

Charles Frederic Roche

- 1 G. H Benton
- 2 Paul D. White
3. T. Z. Cason

*Orlando*

Spencer Augustus Folsom

1. Allen H. Bunce
- 2 E. C. Thrash
3. James D Love

Meredith Mallory

1. W C. Blake
2. John H Peck
- 3 Walter L Bierring

#### GEORGIA

*Atlanta*

Augustus Benjamin Jones (M C, U S A )

- 1 P M Ashburn
- 2 R D Harden
- 3 M W Ireland

*Thomasville*

Ernest F Wahl

1. W. S Thayer
- 2 Sydney R Miller
- 3 Russell H Oppenheimer

#### ILLINOIS

*Oak Park*

William E. Kendall

- 1 Louis L Syman
- 2 Edward W Hollingsworth
- 3 James G Carr

*Peoria*

Orville Barbour

- 1 George W Parker
- 2 Fred M Meixner
- 3 Samuel E Munson

#### INDIANA

*Gary*

Earl Donovan Skeen

- 1 H M English
- 2 C M. Reyher
- 3 Roscoe H Beeson

*Indianapolis*

Edgar F Kiser

1. Herman M Baker
- 2 Bayard G Keeney
- 3 Roscoe H Beeson

#### IOWA

*Des Moines*

Addison Carey Page

- 1 John H Peck
- 2 Tom B Throckmorton
- 3 Walter L Bierring

*Ottumwa*

Frederick Alexander Hecker

1 Edward Tyler Edgerly

2 John H Peck

3 Walter L. Bierring

## KENTUCKY

*Louisville*

Harry Stucky Frazier

1 C W Dowden

2 J Rowan Morrison

3 E B Bradley

James Murray Kinsman

1 C W Dowden

2 Charles G Lucas

3 E B Bradley

Hulbert Viars Noland

1. C W Dowden

2. Charles G Lucas

3 E B. Bradley

Thomas Cook Smith

1 C W Dowden

2 Charles G Lucas

3 E B Bradley

## LOUISIANA

*Morgan City*

Charles Camille deGravelles

1 Daniel N Silverman

2 Charles J Bloom

3 J H Musser

## MAINE

*Portland*

Charles Bradford Sylvester

1 Eugene H Drake

2 Mortimer Warren

3 E W Gehring

## MARYLAND

*Baltimore*

Walter A Baetjer

1 Lewellys F Barker

2 Sydney R Miller

3 Harvey G Beck

John Lanahan Dorsey

1 Lewellys F Barker

2 Sydney R Miller

3 Harvey G Beck

Thomas Barnes Fitcher

1 Harvey G Beck

2 Maurice C Pincoffs

3 Sydney R Miller

Louis Hamman

1 Harvey G Beck

2 Maurice C Pincoffs

3 Sydney R Miller

John T King, Jr

1 W S Thayer

2 Sydney R Miller

3 Harvey G Beck

Lay Martin

1 Thomas R Brown

2 Sydney R Miller

3 Harvey G Beck

A Ferdinand Ries

1 Julius Friedenwald

2 Andrew C Gillis

3 Harvey G Beck

Thomas P Sprunt

1 Lewellys F Barker

2 Sydney R Miller

3 Harvey G Beck

Henry M Thomas, Jr

1 Lewellys F Barker

2 Sydney R Miller

3 Harvey G Beck

*State Sanatorium*

Victor F Cullen

1 Lewellys F Barker

2 Sydney R Miller

3 Harvey G Beck

## MASSACHUSETTS

*Boston*

Helmuth Ulrich

1 William D Reid

2 Conrad Wesselhoeft

3 J H Means

William H Watters

1 William D Reid

2 Edward S Calderwood

3 J H Means

*Waltham*

Dwight O'Hara

1 William B Breed

2 Maurice Fremont-Smith

3 Roger I Lee

## MICHIGAN

*Ann Arbor*

Louis Harry Newburgh

1 Alpheus F Jennings

2 Douglas Donald

3 Charles G Jennings

*Detroit*

- John Everett Gordon  
 1 Alpheus F Jennings  
 2 Douglas Donald  
 3 Charles G Jennings

*Flint*

- Myrton Shaw Chambers  
 1 W. H Marshall  
 2 M S Knapp  
 3 Charles G Jennings

*Grand Rapids*

- Harold Clinton Robinson  
 1 Thomas D Gordon  
 2 Joseph B Whinery  
 3 Aldred Scott Warthin

## MINNESOTA

*Rochester*

- Edgar Vannice Allen  
 1 Philip S Hench  
 2 S Franklin Adams  
 3 George E Brown  
 and  
 E L Tuohy

- David Garrison Ghrist  
 1 A R Barnes  
 2 L G Rowntree  
 3 E L Tuohy

- Charles Koran Maytum  
 1. Fred W Gaarde  
 2 P P Vinson  
 3 George E Brown

*St Paul*

- Edward Schons  
 1 J. A Lepak  
 2 Charles N Hensel  
 3 E L Tuohy

## MISSOURI

*Kansas City*

- Arthur Charles Clasen  
 1. Wilson A Myers  
 2. Lindsay S Milne  
 3 A Comingo Griffith  
 Harry Lander Jones  
 1. P T Bohan  
 2 Frank I Ridge  
 3 A Comingo Griffith

## NEW JERSEY

*Newark*

- L. Charles Rosenberg  
 1 A. E. Parsonnet  
 2 Asher Yaguda  
 3 Harlow Brooks  
 and  
 W. Blair Stewart

*Pleasantville*

- Clyde Mulhollon Fish  
 1. E. J. G Beardsley  
 2 Arthur C Morgan  
 3 W Blair Stewart

*Trenton*

- Barney Doibe Lavine  
 1 J J McGuire  
 2 Wm S Collier  
 3. W Blair Stewart  
 Nathan Swern  
 1. James J McGuire  
 2 William S Collier  
 3 W Blair Stewart

## NEW MEXICO

*Albuquerque*

- John Robert Van Atta  
 1 P. T Bohan  
 2 Logan Clendenning  
 3 L S Peters

## NEW YORK

*Brooklyn*

- Louis Harris  
 1 Maurice J Dattelbaum  
 2 Raymond Clark  
 3 Harlow Brooks

*Jackson Heights*

- Margaret Ruth Reynolds  
 1 Luvia M Willard  
 2 Marshall Carleton Pease  
 3 James Alex Miller

*Long Island City*

- Carl Boettiger  
 1 George Forbes  
 2 Christian Wm Janson  
 3 Harlow Brooks

*New York*

- Louis Faugeres Bishop, Jr  
 1 Louis F Bishop  
 2 William Van Valzah Hayes  
 3 Harlow Brooks

Otto H Leber

- 1 Walter A Bastedo
- 2 Orrin Sage Wightman
- 3 James Alex. Miller

Henry A Rafsky

- 1 Max Einhorn
- 2 George G Ornstein
- 3 Harlow Brooks

Griffith Edwards Thomas (M C, U S N)

- 1 W W Behlow
- 2 L L Pratt
- 3 C E Riggs

*Willard*

Harry Beckett Lang

- 1 C Harvey Jewett
- 2 Harold A Patterson
- 3 John A Lichty

#### NORTH CAROLINA

*Chapel Hill*

Isaac Hall Manning

- 1 L B McBrayer
- 2 W Bernard Kinlaw
- 3 C H Cocke

*Goldsboro*

William Hopton Smith

- 1 L B McBrayer
- 2 P P McCain
- 3 C H Cocke

*Raleigh*

William Banks Dewar

- 1 Paul F Whitaker
- 2 Wm deB MacNider
- 3 C H Cocke

*Sanatorium*

Samuel Moffett Bittinger

- 1 P P McCain
- 2 L B McBrayer
- 3 C H Cocke

*Winston-Salem*

John Kerr Pepper

- 1 Thurman D Kitchin
- 2 L B McBrayer
- 3 C H Cocke

#### OHIO

*Cleveland*

Richard S Dexter

- 1 Harry V Paryzek
- 2 Charles W Stone
- 3 John Dudley Dunham

Charles Thomas Way

- 1 V. C Rowland
- 2 Harry V. Paryzek
- 3 John Dudley Dunham

#### OKLAHOMA

*Oklahoma City*

Hull Wesley Butler

- 1 L J Moorman
- 2 Arthur W White
- 3 Lea A Riely

*Tulsa*

William J Bryan, Jr

- 1 L J Moorman
- 2 Clarence Manning Grigsby
- 3 Lea A Riely

#### PENNSYLVANIA

*Beaver*

Fred Bailey Wilson

- 1 R R Snowden
- 2 George W Grier
- 3 E Bosworth McCready

*Bellevue*

Thomas Alfred Miller

- 1 R R Snowden
- 2 Frederick B Utley
- 3 E Bosworth McCready

*Bethlehem*

Harvey Oscar Rohrbach

- 1 Francis J Dever
- 2 Edgar M Green
- 3 E J G Beardsley

*Lancaster*

Roland Nicholas Klemmer

- 1 Truman G Schnabel
- 2 George Morris Piersol
- 3 E J G Beardsley

*Lansdowne*

Eugene Allen Case

- 1 E J G Beardsley
- 2 Arthur C Morgan
- 3 George Morris Piersol

*Philadelphia*

Mitchell Bernstein

- 1 Arthur C Morgan
- 2 Isadore Kaufman
- 3 E J G Beardsley

Ward Brinton

- 1 E J G Beardsley
- 2 Truman G Schnabel
- 3 George Morris Piersol

Jacob Morris Cahan

1. Alfred Gordon
- 2 Isadore Kaufman
- 3 E. J G Beardsley

Louis H Clerf

1. E J G Beardsley
- 2 Elmer H. Funk
- 3 George Morris Piersol

David Alexander Cooper

- 1 David Riesman
- 2 Truman G Schnabel
- 3 E J G Beardsley

John Thompson Farrell, Jr

- 1 H K Mohler
- 2 Elmer H Funk
- 3 E J G Beardsley

Thomas Fitz-Hugh, Jr

- 1 David Riesman
- 2 Truman G Schnabel
- 3 E J G Beardsley

Arthur Haddon Hopkins

1. E J G Beardsley
- 2 Truman G Schnabel
- 3 George Morris Piersol

Horace H Jenks

- 1 E J G Beardsley
- 2 H Brooker Mills
- 3 George Morris Piersol

Willis F Manges

- 1 E J G Beardsley
- 2 Elmer H Funk
- 3 George Morris Piersol

Samuel Watkins Sappington

- 1 Carl V Vischer
- 2 E Roland Snader, Jr
- 3 George Morris Piersol

Edward A Strecker

1. E J G Beardsley
- 2 Charles W Burr
- 3 George Morris Piersol

William Daniel Stroud

- 1 E J G Beardsley
- 2 Alfred Stengel
- 3 George Morris Piersol

Josephus Tucker Ullom

- 1 David Riesman
- 2 Truman G Schnabel
- 3 E J G Beardsley

Charles Christian Wolferth

- 1 E J G Beardsley
- 2 Alfred Stengel
- 3 George Morris Piersol

### *Pittsburgh*

Ellis Mills Frost

1. J M. Thorne
2. C. W Morton
- 3 E. Bosworth McCready

George Rufus Lacy

1. Joseph H Barach
- 2 J M. Thorne
3. E. Bosworth McCready

Howard Gustav Schleiter

- 1 George W Grier
- 2 J M Thorne
- 3 E Bosworth McCready

Thomas McCance Mabon

1. Joseph H Barach
- 2 J. M Thorne
- 3 E Bosworth McCready

Charles Howard Marcy

- 1 Joseph H Barach
- 2 J M Thorne
- 3 E Bosworth McCready

Cornelius Collins Wholey

- 1 Joseph H Barach
- 2 J. M Thorne
- 3 E Bosworth McCready

### *Wayne*

Henry Field Smyth

- 1 E J G Beardsley
- 2 Charles W. Burr
- 3 George Morris Piersol

### *West Chester*

Henry Pleasants, Jr

- 1 E J G Beardsley
- 2 Truman G Schnabel
- 3 George Morris Piersol

## TENNESSEE

### *Knoxville*

Robert Benton Wood

- 1 O N Bryan
- 2 E R Zemp
- 3 J O Manier

### *Memphis*

Arthur F Cooper

- 1 J B McElroy
- 2 Otis S Warr
- 3 J O Manier

Edward Gilmer Thompson

- 1 Whitman Rowland
- 2 J B McElroy
- 3 J O Manier



## TEXAS

*Dallas*

Henry Morgan Winans

1. D W. Carter, Jr

2 Homer Donald

3 C. M. Grigsby

*El Paso*

Michael Andrew Daily (M C, U S A )

1 R D Harden

2 George R. Callender

3 M W Ireland

James Warren Laws

1 Charles M. Hendricks

2 Will S. Horn

3 C M Grigsby

## VERMONT

*Burlington*

Paul Kendrick French

1 Harry R Ryan

3 C. H Beecher

## VIRGINIA

*Petersburg*

Mason Romaine

1 Milton A Bridges

2 Dean B Cole

3 J Morrison Hutcheson

*Quantico*

Ernest William Brown (M C, U S N )

1 Otis Wildman

2. J. M McCants

3 C E Riggs

*Richmond*

Charles Martin Caravati

1. Paul F Whitaker

2 Dean B Cole

3 J Morrison Hutcheson

James Hunt Royster

1 Dean B Cole

2 Beverley R Tucker

3 J Morrison Hutcheson

*Staunton*

Alexander F Robertson, Jr

1 E J G Beardsley

2 Dean B Cole

3 J Morrison Hutcheson

## BRITISH WEST INDIES

## Jamaica

*Kingston*

Arthur William Grace

1 George A Pemberton Wright

2 C D Briscoe

3 Wm M James

## CANAL ZONE

*Balboa Heights*

Charles Kettig Berle (M C, U S A )

1 P M Ashburn

2 R D Harden

3 M W Ireland

The Executive Secretary reported the following deaths

*Fellows*

Robert H Babcock

Chicago, Ill

June 28, 1930

William P Bowman

Los Angeles, Calif

October 20, 1930

Murrett F DeLorme

Brooklyn, N Y

September 8, 1930

J Edward Harbinson

Woodland, Calif

April, 1930

Preston M Hickey

Ann Arbor, Mich

October 30, 1930

Robert T Hood

Pittsburgh, Pa

October 5, 1930

William J Kay

Lapeer, Mich

April 16, 1930

Guy L Kiefer

Lansing, Mich

May 8, 1930

Joseph Patton

Chicago, Ill

April 16, 1930

Robert Pollock

San Diego, Calif

June 2, 1930

William C Rucker

New Orleans, La

May 22, 1930

Anthony A Rutz

Brooklyn, N Y

May 3, 1928

Cuthbert Thompson

Louisville, Ky

June 23, 1930

Antonio D Young

Oklahoma City, Okla

June 3, 1930

*Associates*

Isidor Betz

Brooklyn, N Y

July 13, 1930

Nicholas Lukin

New York, N. Y

June 10, 1930

Frank C Hollister

New York, N Y

November 30, 1929

The following resignations were accepted  
*Fellows*

Frederick C Harrison	Toronto, Ont
George H Whipple	Rochester, N Y

*Associates*

Aaron C Conaway	Marshalltown, Ia
Anthony H Lange	Detroit, Mich
James B Waddell	Wheaton, Ill

Dr Hugh A Beam, of Moline, Ill, was reinstated as a Fellow of the College

The Executive Secretary was instructed to urge the gift of books of which members of the College are authors to the College Memorial Library, rather than the gift of reprints and miscellaneous articles. It was pointed out that a Memorial Library consisting of books published by Fellows and Associates of the College would be of great interest and worth to the College, whereas reprints are so numerous as to be difficult of suitable housing and indexing, and probably can be very infrequently referred to.

The Executive Secretary reported on a long list of publications contributed to the College Library, the majority of which were reprints. Dr Beverly R Tucker (Fellow), Richmond, Va, had contributed his book, "The Gift of Genius," which was the only book received since the previous Regents' meeting.

The Committee on Hospital Efficiency was by resolution discontinued, because of its lack of activity at the present time.

The work and report of a previous Committee on Postgraduate Medical Instruction was reviewed, and the desirability of having the College maintain a complete outline of all the approved sources of postgraduate medical courses offered throughout the United States and Canada each year was discussed. The following resolution, thereafter, was adopted:

"RESOLVED, that the President appoint a Committee of three to investigate the advisability and feasibility of the College studying the facilities of the United States and Canada for postgraduate instruction."

Dr James H Means, Boston, in the absence of the Chairman, Dr. Jonathan C Meakin, presented a preliminary report for the Phillips Memorial Committee. Thirty-

one theses had been submitted before August 31, for competition for the 1931 award. These theses were still in the process of being read and classified as to rank. The Committee was instructed to consider the present rules governing the award, with a view to revising them, in the light of this year's experience, for future years. The Committee was instructed to consider also the matter of making up the announcement for 1932.

The Executive Secretary presented a financial report on *ANNALS OF INTERNAL MEDICINE*. Heretofore the journal has operated at some deficit, but through increased circulation and the adding of advertising, Volume III, which was completed with the June, 1930, Issue, showed a net surplus of \$554.94.

Reports on the arrangements for the Fifteenth Annual Clinical Session at Baltimore were made by Dr Maurice C Pincoffs, General Chairman of Arrangements, Dr Sydney R Miller, Chairman of the General Sessions, and by Mr Loveland, Executive Secretary. News notes concerning the program will be found elsewhere in this issue of the journal. However, it may be interesting to know that President Miller made a complete analysis of the previous three programs, showing the scope of topics and the names of each contributor. These analyses showed a considerable amount of repetition, not only in subjects, but in the names of contributors. It was the opinion of the Board of Regents, as well as many Fellows of the College, that the Baltimore program should reduce to a minimum the amount of repetition, both in topics and contributors. President Miller reported he had received more than three hundred suggestions of topics and names for the general program, out of which he and his Committee can select only about fifty papers and separate authors.

In further discussion, it was recommended that the Convocation of the College be held on Wednesday evening of the clinical week, instead of Thursday evening. The convocation, being the occasion of the annual address by the President, should be held before the General Business Meeting on Thursday, at which time the new President is inducted.

It was further recommended that a reception by the President and Regents to the new members be held immediately following the Convocation. All newly elected Fellows shall be notified that they are expected to attend the Convocation and the reception, and to come in evening clothes.

After proper discussion, the following motion was regularly made, seconded and adopted:

"RESOLVED, that the President, Officers and Executive Secretary be authorized to furnish any Fellow visiting important medical gatherings with proper credentials."

Fellows of the College desiring letters of identification as official delegates to various important medical congresses should apply to the Executive Secretary for such letters.

President Miller was advised to take under advisement the matter of scientific exhibits, as well as technical or commercial exhibits, at the Baltimore Clinical Session.

Excluding elections made at this meeting, the College membership on November 11 consisted of 6 Masters, 1795 Fellows and 500 Associates, a total of 2301. In point of membership, New York ranked first, with 291, Pennsylvania second, with 206, California third, with 156, Michigan fourth, with 141, Illinois fifth, with 123, Ohio sixth, with 118, and Minnesota seventh, with 104.

Dr Edgar Erskine Hume, a Fellow of the College, proposed a method of indicating Fellowship in the College on the sleeve of academic gowns through the use of a Stafford knot. The matter was briefly discussed, and the following resolution regularly adopted:

"RESOLVED, that Dr Hume's proposal be referred to a Committee of three to report back to the Regents at the next meeting."

Dr Albert A. Getman (Fellow), Syracuse, N. Y., was reported as a new Life Member, as of June 4, 1930.

To meet the requirements of the By-Laws, which state that "it shall be the duty of the Board of Regents to provide a plan for securing an adequate endowment," the Board of Regents regularly adopted the following resolution:

"RESOLVED, that the Finance Committee be authorized to carry on such activities as in

their judgment will stimulate Life Membership."

Members of the present Finance Committee were reviewed, and it was resolved that a new Finance Committee of five, including the two Regents who are now members of the Committee, be appointed by the President, and that the Committee shall be authorized to formulate for the Board of Regents a method for fixing a term of service for a standing Finance Committee.

In order that the provision of the By-Laws shall be carried out in regard to having a joint meeting of the Committee on Credentials for Fellowship and the Committee on Credentials for Associateship, for the purpose of co-ordinating the standards of admission, and also for the purpose of preparing recommendations for election to Associateship and Fellowship at the Baltimore Clinical Session, it was:

"RESOLVED, that the two Committees on Credentials are authorized to hold a joint meeting one month in advance of the Baltimore Clinical Session."

The next meeting of the Board of Regents was set for March 22, 1931, at Baltimore.

Fellows appearing on the program of the Illinois Tuberculosis and Public Health Association were Dr James Stuart Pritchard of Battle Creek, Michigan, Dr Cecil Jack of Decatur, and Dr Fred M. Meixner of Peoria, Illinois.

Dr Pritchard and Dr Meixner discussed the "Causes of Cough" and Dr Jack, "The County Tuberculosis Sanatorium in the City."

In the November Issue of the American Journal of the Medical Sciences, the following Fellows are authors of original articles indicated:

Dr Cyrus C. Sturgis, Ann Arbor, Mich (with Dr Raphael Isaacs) "Treatment of Pernicious Anemia with Desiccated, Defatted Stomach"

Dr William A. Groat, Syracuse, N. Y. "Mitosis in Myeloblasts in Peripheral Blood"

Dr Roger S. Morris, Cincinnati, Ohio (with Dr Stanley E. Dorst) "Bacterial Hypersensitivity of the Intestinal

Tract Its Treatment with Autogenous Vaccine and Sodium Ricinoleate"

Dr Julius Friedenwald and Dr Theodore H Morrison, both of Baltimore, Md  
"A Clinical Study of Gumma of the Liver"

Dr Frank N Allan, Rochester, Minn  
(with Dr Frances R VanZant) "Renal Glycosuria, with Ketosis During Surgical Complications"

Dr Byron D Bowen, Buffalo, N Y  
(with Dr Alvin G Foord) "Acute Interstitial Pancreatitis in Two Cases of Diabetic Coma"

Dr I M Rabinowitch, Montreal, Que  
(with Dr A H Gordon) "Low Basal Metabolism Following Lobar Pneumonia Associated with Marked Undernutrition"

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Dr Lucius C Sanders (Associate), Memphis, addressed the Mississippi County (Ark) Medical Society, September 9, on cancer of the colon

---

Dr Robert A Peers (Fellow), Colfax, Calif, spoke before the San Joaquin County (Calif) Medical Society, September 4, on "What to Tell the Tuberculous Patient"

---

Dr Emmet F Horine (Fellow), Louisville, used as his topic, "The Mechanism of the Heart," in an address before the Third District (Ind) Medical Society at New Albany, October 8

---

Dr Robert M Moore (Fellow), Indianapolis, addressed the Elkhart County (Ind) Medical Society on "Coronary Occlusion," October 2

---

Dr Jack Witherspoon (Fellow), Nashville, Tenn, addressed the Christian County (Ky) Medical Society, September 23, on "Duodenal Ulcers"

---

Dr Elliott P Joslin (Fellow), Clinical Professor of Medicine at Harvard Medical School, was one of the chief speakers at a complimentary dinner given to Francis G Benedict, Ph D Director of the Nutrition Laboratory of the Carnegie Institution of Washington

Dr Colonel B Burr (Fellow), Flint, Mich, was the recipient of the honorary degree of Master of Arts conferred by the University of Michigan Medical School at its eighty-second opening assembly Dr Burr was formerly a member of the faculty and the historian of the University He is the author of "Medical History of Michigan," recently published in two volumes Dr Burr is now retired

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Dr Ernest E Irons (Fellow), Dean of Rush Medical College, Chicago, was a participant in the fifth annual clinic of the Highland Park Physicians' Club held December 4

---

Dr Richard M McKean (Fellow), Detroit, offered a postgraduate lecture on "Hypertension and Nephritis," October 7, in connection with the first series of graduate courses in medicine and surgery offered under the auspices of the Wayne County (Mich) Medical Society

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Dr S Marx White (Fellow), Minneapolis, spoke on "Arthritis Deformans" before the Interurban Academy of Medicine at Duluth, recently

---

Dr John H Musser (Fellow), New Orleans, addressed the Omaha-Douglas County (Nebr) Medical Society on "Oral Cavity in Certain Systemic Diseases," October 20

Dr Musser also addressed the American Protestant Hospital Association at its meeting in New Orleans, October 17-20

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At the twenty-fourth annual meeting of the Seventh District Branch Medical Society of the State of New York, held at Penn Yan, September 24, Dr John L Eckel (Associate), Buffalo, spoke on "Anterior Poliomyelitis," and Dr James E Talley (Fellow), Philadelphia, spoke on "Care of the Heart in Certain Infections"

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Dr George H Spivey (Fellow), resigned, as of September 1, as Director of the Winkler County Health Unit to accept another position of similar nature at Phoenix, Arizona

Dr Thomas B Magath (Fellow), Rochester, Minn, is the Editor of the new American Journal of Clinical Pathology, which will be published beginning January, 1931, under the auspices of the American Society of Clinical Pathologists. Among members of the Advisory Editorial Board, are the following Fellows of the American College of Physicians

Dr Arthur H Sanford, Rochester, Minn  
 Dr Kenneth M Lynch, Charleston, S C  
 Dr Walter S Thomas, Clifton Springs, N Y  
 Dr Charles St John Butler, Washington, D C

The Association of American Medical Colleges held its forty-first annual meeting in Denver, October 14-16. Dr Charles C Bass (Fellow), Dean of the Tulane University of Louisiana School of Medicine, was elected Vice President

Dr Lawrence R DeBuys (Fellow), New Orleans, addressed the Childrens' Hospital Association of America at its annual meeting in New Orleans, October 23, on "Management of a Childrens' Service in a General Hospital"

At the Central States Pediatric Society's annual meeting in Memphis, November 7-8, Dr Maud Loeber (Fellow), New Orleans, spoke on "Evaluation of Gastric Analyses and Stool Examination in a Series of Cases When no other Pathology has been found to Account for Anorexia, Loss of Weight and Capricious Appetite," and Dr John A McIntosh (Fellow), Memphis, spoke on "The Relationship of Metazoal and Protozoal Infestation to Vitamin B Deficiency"

Dr S E Thompson (Fellow), Kerrville, Texas, was elected President of the Southwest Texas District Medical Society at its twenty-fourth semiannual meeting at Corpus Christi, during July, 1930

Dr E Roland Snader, Jr (Fellow), Philadelphia, after having served as Secretary of the Homeopathic Medical Society of the State of Pennsylvania for five consecutive years, resigned from the office at the

meeting of the Society held at Harrisburg, during September. He was elected to the Board of Trustees

Dr G Hardin Wells (Fellow), Philadelphia, was also elected a member of the Board of Trustees

Dr Carl V Vischer (Fellow), Philadelphia, was elected a Censor for a term of three years

Dr David N Kremer (Fellow), Philadelphia, presented a paper entitled, "Obesity Observations on Dietary Management" before the Section on Medicine of the College of Physicians

Dr Howard L Hull (Fellow), Elma, Washington, gave an address on "Public Health Problems in which the Citizen should be Interested," October 25, at Menlo, Washington, before the Federation of Women's Clubs. Some 150 women were present at the meeting

Dr M L Stevens (Fellow), President-Elect of the Medical Society of the State of North Carolina, Asheville, Dr L B McBrayer (Fellow), Secretary-Treasurer of the Medical Society of the State of North Carolina, Southern Pines, and Dr P P McCain (Fellow), Superintendent of the North Carolina State Sanatorium, all delivered addresses at the meeting of the Tenth District Medical Society at Murphy, N C, October 22

Dr McBrayer also addressed the Wayne County Medical Society at Goldsboro, October 3, and the State Nurses Association at Greensboro, October 16

Acknowledgment is herewith made of the receipt of reprints of publications by the following members

Dr J P Zohlen (Fellow), Sheboygan, Wis 2 reprints—"Cardiospasm and Concomitant Esophageal Diverticulum, Case Report" "Echinococcus Cysts of Abdomen and Lung, Case Report"  
 Dr Oliver T Osborne (Fellow), New Haven, Conn 1 reprint—"Medical Education"

Dr Osborne is the author of the following editorials recently published

"The Young Physician," appearing in the MEDICAL JOURNAL AND RECORD, September 3, 1930, page 250,

"Intelligence Tests and Psychology," appearing in the MEDICAL JOURNAL AND

RECORD, also September 3, 1930, page 251

"Medical Education" is another editorial of Dr Osborne that appeared in the September 17, 1930, issue of the MEDICAL JOURNAL AND RECORD

## OBITUARY

Dr Cuthbert Thompson (Fellow), Louisville, Ky, died, June 23, 1930, of pneumonia, aged, 65 years

Dr Thompson was born in Londonderry, Ireland. He attended Magee College, of Londonderry, and Queens College, of Galway. He received his degree of M B, C M from Edinburgh University in 1892. He was Professor of Clinical Medicine at the Hospital College of Medicine and the University of Louisville from 1907 to 1911, Consultant, neurology, Marine Hospital No 11, U S Public Health Service, and a member of the medical staff of St Joseph's Infirmary.

Dr Thompson was a member of his county and state medical societies, a Fellow of the American Medical Association, a member of the British Medical Association, and had been a Fellow of the American College of Physicians since 1919. He specialized in Neurology, and was the author of several meritorious published papers in this field.

Dr Robert Thurlow Hood (Fellow), Pittsburgh, Pa, died October 5, 1930, aged, 43 years.

In the death of Dr Hood, the profession and the community has suffered a distinct loss. Dr Hood was born in Washington County, Pennsyl-

vania, in 1887. After being graduated at Westminster College, he obtained his degree of M D from the Medical Department of the University of Pittsburgh in 1914. He began the practice of medicine in Dormont, a suburb of Pittsburgh, and soon after, making a specialty of internal medicine, opened offices in the Westinghouse Building in this city. During the World War, he served in the Army. Last June he became ill with intestinal influenza, this being followed by a psoas abscess which led to his death. Dr Hood was on the staff of the Western Pennsylvania Hospital, a member of the Allegheny County Medical Society and the Pittsburgh Academy and a fellow of the American Medical Association. He has been a Fellow of the American College of Physicians since 1922. He was a member of the Third United Presbyterian Church, a Mason, and belonged to the Keystone Athletic Club and the Longvue Country Club. Several years ago, Dr Hood married Miss Eleanor Clark, who survives him with three small sons. He is also survived by his father, the Rev R H Hood, and a brother, Thomas Hood, both of Dormont.

—Furnished by E. Bosworth McCready, M D, F A C P, Governor for Western Pennsylvania

# The Biology and Etiology of Cancer\*†

By LEO LOEB, *St Louis, Mo*

THE present era in cancer research dates back somewhat more than 30 years. In this paper I must limit myself to a rapid survey of the advances made during this period and to an indication of how I believe the isolated facts thus accumulated can be combined into a consistent theory of cancer.

To state the essential fact, cancer cells are cells which were originally, either ordinary tissue or embryonal cells, and which, under the influence of environmental stimuli, acting in combination with hereditary factors, assume an increased intensity of proliferation, in some cases this proliferation is combined with increased amoeboid activity, and it is always associated with certain modifications in metabolism and enzymatic activity and with certain other properties. The characteristic feature of this transformation is the peculiar independence of the cancer cells from all those factors which originally caused the transformation. Even before the end stage has been reached, in which the normal cells have definitely become cancerous, the stimuli are

no longer required for the consummation of the change. Various kinds of stimuli—irritating substances, long-continued mechanical irritations, internal secretions—all have in the end the same effect, provided they act on a responsive substratum. They all stimulate growth and as a result of this continued stimulation they lead ultimately to an excessive activity which is continuous and which we call cancer.

In the strict sense we have not to deal with growth substances which are specific in the origin of cancer. Still certain substances are more effective than others in this respect. As to the nature of the latter, Vaubel suggested definite chemical configurations as characteristic of such substances, and Hammett believes that the sulfhydryl group is particularly effective. In general, we can classify growth promoting substances into two classes. (1) Those which take a normal part in the economy of the organism and to which the organism is more or less adapted, as e.g., hormones and perhaps certain contact substances. It seems that these factors if present in the usual quantity produce cancer only in association with hereditary factors. (2) Pathological stimuli to which the organism is not normally adapted, such as extraneous growth substances, e.g., tar, arsenic, and stimulations of a physical nature,

\* (From the Department of Pathology, Washington University School of Medicine, St Louis, Mo.)

† Presented in the Symposium on Cancer before the American College of Physicians, Minneapolis, Feb 13, 1930.

acting as prolonged irritations To these agencies the organism responds more readily with pathological growth processes, which, step by step, may pass into cancer

Growth substances of the second type, namely, those to which the body is not adapted, may act not only on adult tissue, but under certain conditions, they can transform also embryonal tissues into cancer, as shown by the experiments of Askanasy, who used for this purpose lipoid solvents, and of Murphy and Landsteiner, who added tar in great dilution to embryonic chick tissue and injected the mixture into adult chickens But successes are only exceptional and they seem to be limited to embryonic tissue implanted into adult organisms All other farther going claims have not so far been confirmed

Above we have referred to the importance of the substratum, on which the various stimuli act As far as we can judge at the present time, the rôle that heredity plays in the etiology of cancer is probably that of making the substratum more responsive to the stimulating agencies A sensitized tissue, as for instance, the uterine mucosa sensitized by the corpus luteum, responds with increased intensity to various mechanical and chemical stimuli, to which a normal tissue would remain almost indifferent It will not be necessary for me to discuss in a more detailed way the mode of action of heredity in cancer, inasmuch as this problem will be discussed later by two competent investigators, Dr Wells and Dr. Warthin However, inasmuch as my own studies, for many years past, have dealt with this problem, I may

perhaps be permitted to make two further remarks In the first place, as stated, I believe that, in the production of cancer, heredity interacts, in the large majority of cases, with various stimulating factors in a wide range of combinations At one end of this range the external factors are acting with such intensity that they alone, or almost alone, can call forth the cancerous transformation, at the other end, hereditary sensitization of the tissues is so intense that ordinary metabolic changes or slightly abnormal ones, such as would be innocuous in an ordinary individual, can lead to the production of cancer Midway between these two extremes we find all kinds of quantitatively varying combinations

Secondly, cancer in this respect does not differ from a large number of other diseases, in which we also find such varying combinations between hereditary and environmental factors

During the process of transition from a normal to a cancer cell, the former acquires step by step some new properties, as far as structure, metabolism, proliferation and ameboid activity, chemical constitution, and transplantability are concerned Above all, to emphasize the essential point, the cell assumes an increased proliferative activity, and often an increased ameboid activity, it penetrates into the surrounding tissue, is carried away by the blood or lymph stream and produces metastases in different places

If we transplant cancer cells from one individual into other individuals of the same species and strain, it is possible, in the case of a certain number of tumors, to make them grow in the strange hosts and to transplant them



indefinitely from generation to generation into other organisms of the same strain. However, in the case of other tumors, such transplantation does not succeed; the cells behave like normal tissue cells and can be transplanted only into the animal in which they originated. Between these two extremes all kinds of intermediate conditions exist. In transferring those tumors which can be readily transplanted, we quite commonly notice that a gradual increase in growth energy takes place in the course of the first transplantations, even through ordinary mechanical stimuli the growth can be increased. Similarly through the use of certain injurious factors the growth energy can be depressed. In experiments carried out with M. S. Fleisher, we could furthermore show that it is possible to a certain extent, to immunize cancer cells against the effect of certain substances and that this change is transmitted to subsequent cell generations.

The transplantability of tumor cells from generation to generation proves that they are potentially immortal, but inasmuch as they are merely transformed tissue cells the tissue cells themselves from which they originated are also potentially immortal, a conclusion which has been confirmed by long-continued growth of fibroblasts in tissue culture. Not in the potential immortality, therefore, do tumor cells differ from ordinary tissue cells, but they differ from the latter in their constant excessive activity and in their resistance to the toxic factors active in homoiotransplantations, to which normal cells succumb.

In this connection I might emphasize once more the great importance of

transplantation as a method in tumor investigation. Transplantation is not merely an imitation of metastasis formation as is occasionally stated. Metastases are autotransplantations occurring under uncontrolled conditions. Transplantations can be defined as homoiometastases produced at will, experimentally, under controlled conditions. This method is indispensable in tumor investigations. It makes possible not only the study of the specific character of tumor cells, but it is necessary also as an instrument in the analysis of the character of the cancerous transformation.

By means of this method there was discovered one of the most important effects of cancerous growth, namely, that of stimulating other tissues with which the cancer cells are in contact also to become cancerous. Such a contact action is not an exceptional occurrence. Strange as this effect may appear, related growth-promoting contact substances are normally given off by the so called organizers which play such an important rôle during embryonic development, even during adult life such substances regulate the interaction of tissues and according to their character either stimulate or inhibit growth phenomena.

Should it not be possible to extract experimentally these growth promoting contact substances directly from tumor cells and transfer them separately from the latter into other individuals and thus produce cancer? Our first experiments in this direction with a rat sarcoma were unsuccessful. While filtrates through filter paper, which did not hold back the cells, produced tumors, filtrates through Berkefeld filters

did not. A number of years later Peyton Rous showed that in the case of sarcomata found in chickens, cell-free filtrates injected into other chickens gave rise to similar sarcomata. This proved to be an extremely important finding, which, apparently, depended not on the transfer of a living filterable microorganism but on that of a chemical substance inciting growth.

There is, therefore, no doubt that, in certain cases, agents distinct and separate from tumor cells can produce a cancerous transformation of normal cells. Subsequently the attempt has been made to effect a similar separation of an agent from tumor cells in the case of various mammalian cancers. While we cannot deny that it may be possible to accomplish such a result, it seems to me that a definite proof of it has not yet been given. It appears, furthermore, that also in the case of the experimentally produced tumors in fowl, in which certain investigators believed they had demonstrated the presence of such an agent distinct from cells, the actual proof still awaits confirmation.

While thus, as far as we can see at present, the existence of a separate agent causing tumor formation has been demonstrated with certainty only under two conditions, namely, in the case of the contact cancerous transformation and in the chicken sarcomata, we must consider it probable that similar organizer-like substances are active also in the case of other tumors and that perhaps future methods of research will establish their existence.

In tissue cultures, A. Fischer and his associates have observed that cancer cells, while they may not grow more rapidly than normal regenerating cells,

have the power to outgrow the latter in the end and usually to destroy them.

The injurious action exerted by cancer cells, under these conditions, is probably due to abnormal products of metabolism given off by tumor cells or to abnormal enzymes. Such an abnormal metabolism of cancer cells has been discovered in recent years by Warburg and it has been found also in tumors growing in the living animal by Cori. In tumor cells, as in yeast cells, the enzymatic splitting of carbohydrates and the production of lactic acid by this means is very marked, not only under anaerobic but under aerobic conditions as well. Although these findings are of great interest and importance, still they do not absolutely differentiate cancerous from normal tissues. In particular regenerating tissue approaches in this as well as in other respects cancer very closely, even more so than does embryonic tissue. Again we notice that no sharp line of demarcation exists between normal and cancerous tissues.

There is, however, an interesting set of phenomena, which seem to point to a somewhat greater difference between malignant tumors and normal cells, namely, their behavior in immunity. As we have stated above, cancers, like normal tissues, can almost invariably be transplanted into the same organism (auto-transplantation). In a number of cases they can be transplanted also into other individuals of the same strain. This may be due partly to their increased proliferative activity, but probably also to a change in their individuality or organismal differential, that which differentiates the various organisms from each other. In addition, a

change in the organ differential, which differentiates the various tissues and organs within the same organism, may be involved. The latter conclusions are based mainly on three lines of evidence, namely, (1) On the fact stated above, that many tumors, in contradistinction to normal tissues, can readily be transplanted into other animals of the same species and that from generation to generation of cancer cells the excessive cell activity persists. (2) On the experiments of Lumsden, who believes he has been able to differentiate between that type of immunity against transplanted (homoio) tumors which is directed against substances which these tumors have in common with other cells of the same organism and species, and the type of immunity which is directed against substances which all cancers have in common and which is independent of individual and species differentials. Therefore, tumor cells must differ in their chemical constitution from normal cells of the organism in which they have developed. (3) On experiments by Hirszfeld, Witebsky and Lehmann-Facijs, who found, in cancer, antigens of a lipoid character, and in this case, also, according to the latter investigator, these antigens are of two kinds, namely, those bearing the organismal and others bearing the organ differential. It seems furthermore that, in cancer cells, antigens originate which have certain constituents in common with the heterogenetic antigens.

These observations seem to sustain a suggestion made by Tyzzer and the writer many years ago, namely, that cancer growth may be conceived of as due to a somatic mutation, which signifies a change in the gene constitution of

a few localized cells, this mutation would explain the persistence of the characteristics which tissue cells assume when they become transformed into tumor cells. Such a somatic mutation is to be distinguished from a germinal mutation, which latter affects the germ cells and is responsible for hereditary changes in the organism as a whole and is transmitted from generation to generation of organisms. In harmony with the assumption of somatic mutation are also the recent experiments of L. C. Strong, who found that two tumors originating in the same mouse and, therefore, originally endowed with the same individuality differential, behaved differently from each other in the course of transplantation into the same types of hosts and in particular did they show a different behavior according to the sex of the host.

There is some reason for assuming that such an acquired difference in the organ and organismal differentials of certain localized tissues may alter their relationship to the neighboring tissues. The normally existing restraining contact substances of an autogenous character may not function typically towards abnormal tissues and the affected tissues may be uninfluenced by the normal regulating and restraining hormones, these disconnected tissues would thus grow as a more or less independent organism within an organism. This circumstance together with the other acquired characteristics, in particular the increased growth energy of cancer and the changed metabolism would explain the peculiar behavior of cancer cells. With this change would go hand in hand a more active production of growth promoting substances, which

would constantly renew themselves inside the proliferating cells and spur on the latter to continued excess activity under abnormal conditions. It appears as if the activity of these cells automatically leads to the new production of such substances, and thus we would have to deal with processes autocatalytic in their action. Furthermore, it seems that in certain cases such substances can be extracted from the cancer cells and exert their effect on neighboring tissues.

While transplantation and other methods give us an insight into the distinctive features of cancer and normal cells and into the changes which take place in normal cells during cancerous transformation, they do not furnish us directly with an understanding of the factors which bring about this transformation. In this we have to deal with an entirely different problem and we have shown that here hereditary factors in combination with various growth-promoting agencies play the main rôle. But in this case the hereditary factors concern the germ cells and the genes located there, and furthermore germ cell mutations may perhaps be responsible for the hereditary predisposition to cancerous transformation. Both the germ cell changes as well as the somatic changes are hereditary, but each in a different way and each must be studied by different methods. If we interpret, tentatively at present, the action of heredity as sensitizing the substratum to the effect of various growth-promoting agencies, then we may conclude that all the factors which cause cancer have in common that they increase the proliferative activity of cells usually over a long period of time and we may

conclude that it is this continued excess in proliferative activity in localized and often in sensitized cells which leads in the end to the cancerous transformation.

I cannot close without discussing briefly the possible significance of micro-organisms in the etiology of cancer. Recent investigations have not tended to lend support to the view that micro-organisms may be the essential cause of this condition—a cause which acts perhaps in combination with other factors, as Gye and Barnard assumed. On the whole, the repetition of Gye's experiments by other investigators has not confirmed the facts on which this assumption is based. Neither do other claims in this respect seem to be much better founded. If micro-organisms should play a part in the etiology of cancer, this part is probably none other than that played by higher parasites, such as spiroptera of Fibiger, in the case of carcinoma of the forestomach of rats, and the *cysticercus crassicolis* with which Bullock produced sarcoma in the liver of rats. These parasites apparently give off substances which stimulate the surrounding tissue cells to undergo cancerous transformation. But they are not concerned in the growth of cancer cells as such, and they do not, as far as we know at present, provide the constant stimulus which spurs on the formerly normal cells to grow as cancer cells continuously, and without which the cancerous tissue would resume a normal growth. The bacteria present in the crown gall of certain plants may perhaps play such a stimulating rôle, but there does not exist convincing evidence of a similar

kind in the case of mammalian and in particular of human tumors

It might be possible to think of the chicken sarcoma agent, or of the agent that causes the development of contact cancers—as when a sarcoma develops in contact with a carcinoma—as filterable micro-organisms, but what we know of the character of the chicken sarcoma agent fits in as well, or even better, with the idea that it represents a complex organic substance, presumably of a colloid nature.

In view of all the other data, which we possess, as to the etiology of cancer, the theory which I have presented in this paper seems to me much more probable, at the present time, than the assumption that, in the cases mentioned, a living micro-organism is transferred. What we know of the rôle of extraneous growth substances, and of internal secretions, in the etiology of cancer, and of their interaction with heredity, all these well established facts do not seem very well compatible with the assumption that micro-organisms are the essential cause of cancer, and that cancer is therefore merely a peculiar type of an infectious disease. Furthermore, what we know of the behavior of transplanted tumors and of immunity in cancer, does not lend support to that view.

All these facts are compatible, however, with the conception that certain growth stimuli acting in association with hereditary factors, which latter may perhaps sensitize the cells to the action of the growth stimuli, cause a gradual transformation of normal into cancerous cells. During this process the

cells step by step assume characteristics which are very similar to those which regenerating cells possess, but these characteristics are even more accentuated in the case of cancer cells than in the case of ordinary regenerating cells. Whereas in the case of regenerating cells these changes are temporary—the cells soon returning to the equilibrium of normal tissue—in the case of cancer these properties, once acquired, are permanent. The mechanisms underlying these properties are constantly reproduced within the cells thus affected, and are transmitted to succeeding generations indefinitely. This transformation leads to a new state of cell equilibrium which potentially exists in all cells which have the ability to proliferate. In the course of this transformation, certain changes of a delicate nature take place in the chemical constitution of the cells, the transformation seems, to a limited extent, to affect those chemical processes on which the individuality and tissue differentials depend, and inasmuch as we have to deal with a definite change transmitted in the same way from cell to cell generation, we may assume that the fixed cell constituents, which determine these biochemical properties, are permanently altered. We may, therefore, conceive of this process as a somatic mutation, a mutation occurring in certain ordinary tissue cells. At the same time, we must assume that the proneness to undergo this somatic mutation depends largely, but not entirely, upon the genetic constitution which these somatic cells received from the germ cells.

# The Influence of Heredity on the Occurrence of Cancer in Animals\*

By H GIDEON WELLS, *Chicago, Illinois*

**I**N order to keep within the time limit I propose to present my material in the form of a brief synopsis to be followed by a series of lantern slides which will serve to illustrate some of the points I hope to make

The justification of speaking on the subject of cancer in animals before a group of men interested in human medicine lies in the fact that it would seem that our best prospect of obtaining reliable information concerning the influence that heredity may play in the occurrence of cancer will come through the study of cancer in animals. All hereditary studies in man are difficult because of the long period between generations, the small families, and uncertainties of diagnosis. To be sure, we can learn and have learned some things concerning the relation of heredity to the occurrence of cancer in man, and Dr. Warthin will speak of these

To get the matter under adequately controlled conditions so that we can repeat our observations and verify them, it becomes necessary to study the disease in animals.

Before we can utilize the returns of

this sort of procedure, we have to establish certain facts. First, that cancer in animals is the same disease that it is in man; and, second, that the rules of heredity are the same in animals as in man.

In the beginning of our studies of experimental cancer, much doubt was thrown on the proposition that the disease that we were studying in animals was identical with human cancer. There are certain differences to be observed between different species in respect to incidence and behavior of cancer, but as we have learned more and more concerning animal cancer, these doubts have been dispelled, so that it is now safe to say, I think, that there is no reasonable doubt that fundamentally cancer is the same in all species of animals, although differences occur between different species.

In the other matter, as to the identity of the laws of heredity in man and animals, we have only to recall the fact that the principle of genetic transmission of character was discovered by Mendel, working with plants; that these principles, lost for thirty-five years, were rediscovered by botanists working with plants; that immediately the zoologists took up the matter they found that in all species of animals to

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\*Presented in the Symposium on Cancer before the American College of Physicians, Minneapolis, Feb 13, 1930.

which they applied these principles the laws were found to be the same, and that we have no reason to suppose that what holds for all other multicellular living forms will not hold for man. As a matter of fact, we all know that certain conditions are inherited in man exactly as other conditions are inherited in animals, for example, the classical case of color blindness which obeys very definitely the Mendelian principles.

The study of the influence of heredity on the occurrence of cancer in animals may be carried out in several ways, one in a broad way, is by comparative pathology. There are very distinct differences in the occurrences of different sorts of cancer in different species. Why should different species behave differently? They are different species through heredity, of course, and the fact that in swine a common tumor is a mixed tumor of the kidney, that in sheep primary epithelial tumors of the liver seem to be particularly common, that in mice mammary gland tumors are particularly common, in rats the usual growths are sarcomas, illustrates hereditary differences in species in respect to the occurrence of cancer.

To me, particularly striking is the domestic cow. In most mammals one of the commonest sites for the occurrence of tumors is the mammary gland. Of all species of mammals there is none in which the mammary gland is subjected to so much over-stimulation, abuse, traumatism, and so on, as the dairy cow, and yet there are practically no cases, so far as I know only two cases have ever been described, of cancer in the mammary gland of cows. That sort of thing is related to the well known

human fact that fibroid tumors of the uterus seem to be particularly frequent in the negro, and there are other instances that might be cited.

The experimental study of the relation of heredity to cancer in animals can be carried out in two ways. One by the study of transplanted tumors. Thirty years ago Dr. Loeb and Dr. Jensen contributed a great deal to cancer research by their discovery of the possibility of series transplantations of cancers. We have learned much about cancer through that method. But in regard to heredity, it does not seem to offer us so much, for the reason that the principles that determine whether a transplanted cancer will grow in another animal from the one which furnished the original cells seems to be something entirely different from the principles that determine that a given animal will develop a cancer from its own cells, and it has been found experimentally that the behavior from the genetic standpoint of transplanted cancer is very different from the behavior of spontaneous cancers.

The other way is to study the occurrence of cancers arising spontaneously in the ordinary course of the animal's life, or cancers produced by stimulation with tar or other means. These things come nearer the human problem and are being studied zealously in many places.

At the present time we cannot present a complete picture of how heredity does modify the development of spontaneous cancers in animals, but this much has been established, and I think is pretty generally agreed that the study of experimental animals has shown beyond any question of doubt

that heredity does play a very great rôle in determining not only whether animals will or will not develop cancer, but where they will develop it, that is in what organ, and also the type. For example, certain strains of mice produce cancers almost exclusively in the mammary gland, but it is possible to find strains of mice in which the tumor is predominantly in the lung, and to produce strains of mice in which the tumor is predominantly a sarcoma arising at the point of injury. That seems to be adequately established.

It also is established that heredity may determine whether cancer will or will not arise from a fairly constant type of injury. For example, in Dr. Wood's laboratory the demonstration that the infestation of the liver of rats with certain parasites leads to sarcoma, was followed by the demonstration that certain strains of rats would show this condition very much more frequently than other strains which seemed to be relatively immune from the development of malignant tumor, although their livers were equally infested with parasites.

So these things add up to what Dr. Loeb has already told you, that the combination of the genetic background and the stimulation are together the essential things. In fact, I think that was expressed best years ago by Dr. Loeb himself, in this very simple equation. that cancer is the product of heredity by stimulation. It is perfectly evident in this simple equation that you can get the same end result, whether the heredity factor is large and the stimulation small or the stimulation large and the heredity factor small  $H \times S = C$ .

It is a question, perhaps, whether the hereditary resistance to cancer is ever so great that it will resist all attempts at production of cancer, but certainly there are cases where the heredity factor is so large that any ordinary amount of stimulation such as occurs in ordinary life without obvious injury may fail to result in cancer. On the other hand, the inherited lack of resistance to cancer may be so marked that cancer occurs with a minimum of antecedent injury. I might refer to gliomas in man, which occur early in life, not the result of any obvious trauma, but apparently entirely determined by heredity.

Those are the main points, or as much as I can give you in the time at my disposal. I should like to show a few slides to illustrate some of these points.

First of all, the fact that cancer is the same thing in animals as in man. Here, for example, is a carcinoma of the stomach in a mouse. That brings up another difference due possibly to heredity, or possibly to other factors in the production of cancer, that man is the only species in whom cancer of the stomach is not the greatest of rarities, whereas in man we all know it ranks first. This is one of the few known cases of glandular carcinoma of the stomach in the mouse, and it is in structure quite the same thing as carcinoma of the stomach in a man, you see.

The animal cancer that has been most studied in laboratories is the mammary gland cancer of mice. Here is shown a cancer developing in a lactating mammary gland. If you compare the normal lactating mammary gland with the carcinoma, you see it shows about the same sort of differences you are accus-



tomed to seeing in human mammary cancer. They behave in all respects the same.

Here is a mouse carcinoma invading the wall of a blood vessel, producing a tumor thrombus from which emboli may escape to other parts; for example here in the lung is a tumor embolus. Certain strains of mice will develop secondary tumors in the lung, and others will not irrespective of whether the emboli go there or not. In certain strains the emboli go there and die, in other strains they multiply and you find the lung filled with tumor metastases, as here. In other words, the behavior in respect to metastases and all that is the same in these animals as in man.

Here are metastases of a mammary gland cancer occurring in the liver of a mouse. You see the same picture that you are familiar with in human cancers. Again, here is seen a tumor metastasis from a cancer of the lung of a mouse involving a bone and leading to a pathological fracture. Also we see mouse cancers invading a lymph node, passing through the lymphatics as do human cancers.

Not only do the carcinomas occur in the mammary gland of these mice, but they occur elsewhere in the same sort of way. For example, here are sections from a mouse that had an ulcer following a wound of the skin. Then on that ulcer, just as might happen in an ulcer in a man, is seen a squamous cell carcinoma that has invaded and is spreading beneath the overlying skin, to illustrate that cancers occur under the same conditions in mice and man.

This mouse had a broken tooth which irritated the mucous membrane, and here is seen the squamous cell car-

cinoma of the mouth that developed. In this case it has invaded the base of the skull and is producing pressure on the central nervous system, just as such a carcinoma might do in a man.

Here are sections from another mouse that had a prolapsed rectum for a long time, and in that prolapsed rectum first occurred epithelial metaplasia, and then this condition, carcinoma.

Mice have basal cell carcinoma, as shown in the next slides, so-called rodent ulcer type of carcinoma. The interesting thing is that they are so identical with the behavior in human species that they are seen chiefly in very old mice. This picture shows an extremely old mouse that had his face eaten away by basal cell carcinoma. Histologically these growths present the same character as in man, and also the same character of not tending to produce metastases.

Not only do these animals have carcinomas, but they have sarcomas. Here is a round cell sarcoma of a mouse. You see it is quite the same picture as a human round cell sarcoma, and the next few slides illustrate the fact that mice have the various histological types of sarcoma seen in man.

Also benign tumors occur. For example, here is an adenoma of the ovary of a mouse, and here are uterine fibroids. In fact, I have seen in mice nearly every tumor that I have ever seen in the human species, with few exceptions. So then we have to admit that tumors are essentially quite the same in all species.

As I have said, the transplanted tumors in mice are different in many respects from the spontaneous tumors. One essential difference is that many

transplanted tumors will grow for a time and disappear spontaneously, differing fundamentally from spontaneous tumors in this respect. Whether a transplanted tumor will take or not depends upon something about the reaction of the individual to foreign cells, a factor that is not present in the spontaneous tumors. Consequently, it is not strange that we have found that the study of transplanted tumors shows them to obey different laws from the spontaneous tumors.

Our great hope, I think, lies in the new developments that have come through the work of Yamagiwa in producing carcinomas in animals by irritation of the skin by tar. It thus becomes possible to produce at will cancers in animals from their own cells, analogous to cancers arising in man, and to study the hereditary influences. This work is new, but much probably will come of it.

I cannot go into the details of the mechanisms by which heredity determines the occurrence of cancer. That is not yet agreed upon. Miss Slye, with her large material, has observed in her experience that susceptibility to cancer behaves as a Mendelian recessive, and that resistance is dominant. Other workers are not ready to accept this view and present evidence which they interpret to the contrary, so we will have to consider that this subject is still unsettled. The important fact now available is that it seems to be fully established that heredity does play a large rôle in determining whether an animal will have a cancer or not, and what sort of a cancer it is likely to be.

Miss Slye has shown that it is possible to produce from mice with cancer, bred with non-cancerous mice, different

strains, some of which will show cancer and others not. She has produced strains like this that have gone for twenty-five or thirty generations with never a cancer in them, whereas other offspring of the same original mating produced cancer regularly. But more important for the human problem, is her production of strains in which the cancer crops out after intervals of several generations. For example, in the chart here shown, are several intervening generations without cancer, but it appears again, and then it disappears. This behavior is entirely analogous to what is observed with recessive inheritable qualities generally. This sort of thing Miss Slye interprets as indicating that cancer behaves as a recessive character.

There are other illustrations of similar behavior of neoplasm. For example, Miss Stark, working with a fruit fly, has produced a type of fruit fly in which a growth resembling a melanotic tumor appears in one half of the male larvae, and in this behavior it shows susceptibility as a recessive, as Miss Slye's work with the mice indicates.

We seem justified in saying that the study of heredity in cancer will probably have to be carried on largely with animal material, from which we may hope to learn how to understand the things we already have observed and will observe in the future in regard to the relation of heredity to cancer in man. A good start has been made. So far the main result of the work is, as I see it, to settle beyond question that heredity does play an important rôle. The ways in which the heredity brings about the susceptibility or resistance to cancer remain to be determined.

# Heredity of Carcinoma in Man\*

By ALDRED SCOTT WARTHIN, *Ann Arbor, Michigan*

IF one may judge from the literature, all of the animal experimental work on the heredity of cancer susceptibility has not made a very deep impression on the general medical mind, because in very few textbooks on pathology and special works on cancer, and in the propaganda literature of associations for the prevention or control of cancer, very little, if any, emphasis is laid upon the part played by heredity in the etiology of neoplasms. As far as our present statistics concerning the heredity of cancer in man are concerned, I believe that they have very little value indeed. No statistical problem offers greater difficulties than that of the incidence of family susceptibility to cancer in the general population. The average hospital case-histories throw but little light on this question, even in specialized teaching hospitals in which the taking of clinical histories is supposed to be more or less supervised from a teaching standpoint, the histories of individual cases of cancer usually contain no information as to the multiple incidence of cancer in the families of the cancer patients. During the years 1907-1909 I collected from the histories of the Surgical Department of the University Hospital what

data I could find relating to the multiple incidence of neoplasm in the families of patients who had been operated upon for carcinoma. In the ordinary run of case histories from the surgical clinic, it was found that less than one per cent of such cases gave any family history of cancer at all. When, however, these same cases were investigated by a special method, in the form of letters or personal communications with the family of the patient, this percentage was raised to over fifty per cent.

The bald question, directed to the patient himself as to the occurrence of other cases of cancer in his family, is very often unproductive of positive information. The affected individual has very frequently about the same attitude towards revealing any family history of carcinoma that he has towards giving any history of syphilitic infection, or of the inevitable sexual phenomena of old age. Many have a certain horror or a fear of the stigma attaching to a family history of multiple incidence of neoplasm. Moreover, there are relatively few individuals in the average hospital population who know their own family history back of the immediate parental generation. It is a very great mistake to depend upon the patient himself for the essentials of a family history. Other members of the

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\*Presented in the Symposium on Cancer before the American College of Physicians, February 13, 1930

family should be questioned. Further, very few hospitals pay sufficient attention to the importance of having the interne make special inquiry as to multiple family incidence of neoplasm. The importance of the constitution and of hereditary susceptibility is not yet recognized by the average practitioner or medical teacher of today; and this fact is reflected in the inadequate case-histories made by the average interne. In addition to the imperfections of history-taking, cancer statistics are further vitiated by the great frequency of both positive and negative incorrect diagnoses.

The first slides shown present examples of the multiple incidence of cancer in the families of carcinoma patients operated in the University Hospital prior to 1908, and represent the results of special investigation made to ascertain the occurrence of multiple cancers in the families of given patients. It will be seen that as a rule not more than three generations are represented. Some of these family histories are incomplete in so far as they do not include all of the non-cancerous members of the family. Moreover, some of the "cancers" of the first generation represent family tradition only, the organ or tissue specifically involved not being known. A collection of such histories showing the multiple familial occurrence of cancer was published in a paper by me on "Heredity with Reference to Carcinoma" in the *Archives of Internal Medicine*, 1913. There were 330 cases included in this investigation and over 50 per cent showed a multiple incidence of carcinoma in different generations. In the remaining 50 per cent of cases in which a history of multiple

incidence could not be obtained, this failure was due almost wholly to the ignorance of the patient or other member of his family concerning his family history as far as the cause of death of the various members was concerned. That a positive history of multiple incidence of neoplasm in the same family could be obtained in 50 per cent of cases by means of special investigation speaks strongly in favor of an hereditary family susceptibility.

These collected examples of multiple familial incidence of cancer showed a number of interesting things. In some families the carcinoma cases appeared in every generation, indicating a direct inheritance. In other families the cases of cancer may skip a generation, or even two, the cancer-cases appearing in the collateral lines, and not in the direct line for one or two generations. To the generations showing multiple occurrence of cancer cases I applied the name, cancer fraternities or cancer generations. The collected charts show that carcinoma may be passed on through the direct line, or through the collateral lines, and may appear in every generation, or may skip one or two generations (See Fig 1)

In certain families the incidence of carcinoma becomes so marked, the cases so crowded, that these can be properly designated as cancer families. For instance, one family shows two cases in the first generation, four in the second, and two in the fourth, the incidence being so great as to stigmatize this family as a "cancer family." In this family the maternal grandmother died of "tumor." Her non-cancerous brother had two children both of whom died of "tumor." Her son married a woman

NO. 6

Cancerous Fraternities.

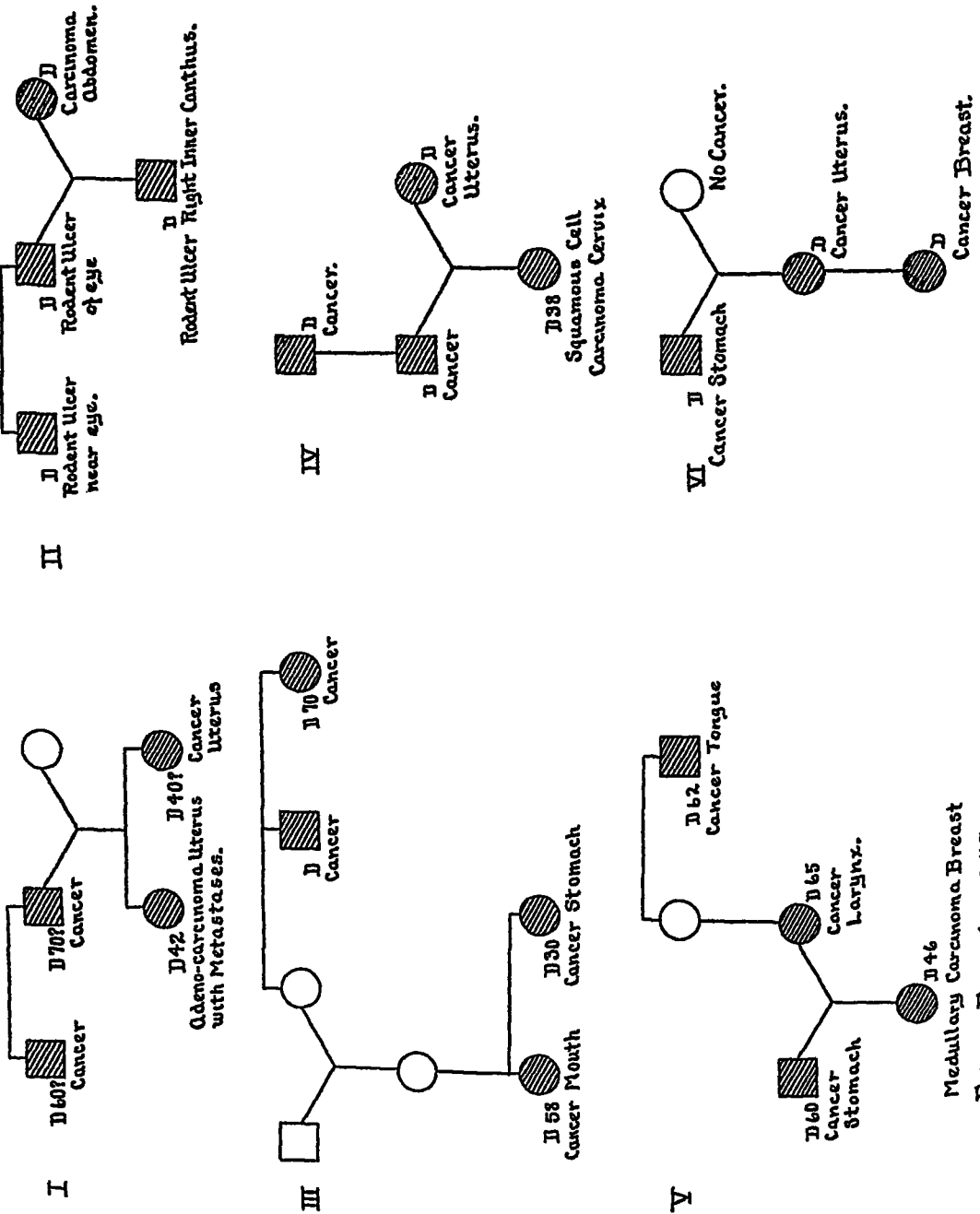


FIG 1. Examples of "Cancerous Fraternities" Multiple family incidence of cancer

who had two brothers die of cancer of the stomach. Neither the son or his wife developed cancer, but they had only three children, daughters, who all died of malignant tumors, in two cases of the uterus, and in one case of the ovary. In Family O (Fig. 2) the collateral transmission of cancer is well shown. In Family P (Fig. 3) there were 8 cases of carcinoma in three generations, the inheritance being both collateral and direct. In the third generation of 13 children, three daughters died at relatively early ages of cancer of the breast, while 5 brothers and 5 sisters died of tuberculosis before the age of thirty. This association of a family susceptibility to tuberculosis with that to carcinoma we have repeatedly noticed in our material. In Figs 4 and 5 other examples of this association are shown.

Since 1913 this laboratory has collected a large number of family records showing the multiple incidence of neoplasm. One fact stands out very prominently in these records, and that is the tendency for the carcinoma to be localized in certain organs or systems, as for example, the gastro-intestinal tract or the sexual organs. In a given family the affected males may show carcinomas of the gastro-intestinal tract and the females carcinomas of the sexual organs, particularly breast and uterus. There is apparently a local *organ* or *tissue susceptibility* inherited. In Family S (Fig. 6) the great grandfather died of cancer of the stomach. His son also died of cancer of the stomach after marrying a woman who died of cancer of the breast. They had six children, all of them dying of cancer, three daughters of cancer of the breast, two sons of

cancer of the stomach, and another son dying of abdominal cancer not precisely located. The youngest son married a woman without a family history of cancer. They had one child, a daughter, dying at 36 of cancer of the uterus. In Fig 7 the predominance of cancer localized in the sexual organs is shown. This inheritance of a local predisposition to neoplasm is especially marked in the case of the so-called glioma of the retina (retinoblastoma). The observation of Purtscher (Fig 8) is an example illustrating this point. From a grandfather who had sarcoma of the arm, there were 11 children, three of who had retinal glioma. From one of these gliomatous daughters, there came a son with glioma; and from another normal daughter there came two gliomatous sons. Instances are recorded of some of the glioma families in which all of the children have been affected. In one family there were 13 cases of glioma in two generations, and in another 18 cases in three generations.

In some families a distinct inheritance of two organ susceptibilities has been observed, as for example, cancer of the respiratory tract and cancer of the genito-urinary organs. Very frequently this local organ predisposition to cancer shows a sex-limited inheritance. In Fig 9, the family chart shows a predilection of cancer for the larynx in the males, and for the breast in the females.

In 1913 I reported the study of a German family living in Washtenaw County, Michigan, in which up to that time there had occurred 18 cases of carcinoma in three generations (see Fig. 10). In 1925 I made a more complete study of the same family (*Jour*

# CANCER FAMILY O

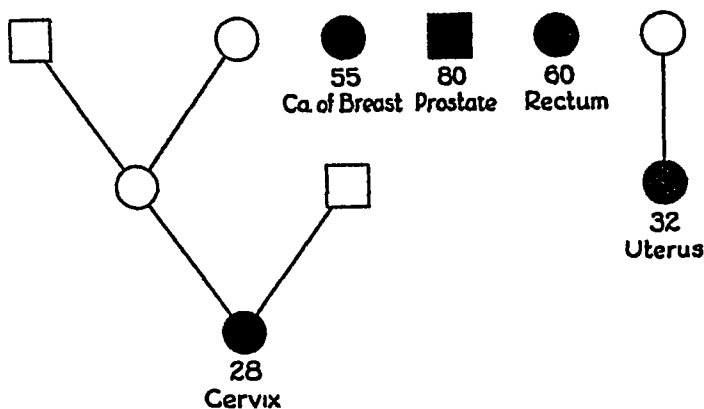


FIG 2 Multiple family incidence of cancer in the collateral lines

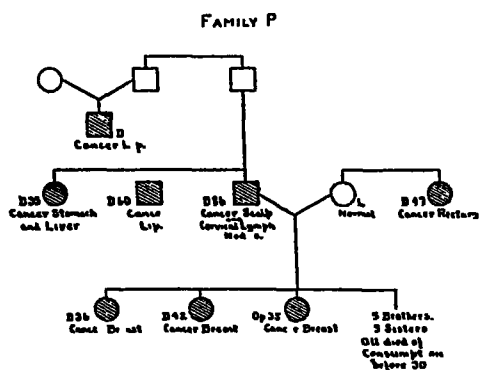


FIG 3 Multiple family incidence of cancer Two local predispositions shown Gastro-intestinal tract and breast Also the associated susceptibility to tuberculosis

# CANCER AND TUBERCULOSIS FAMILY

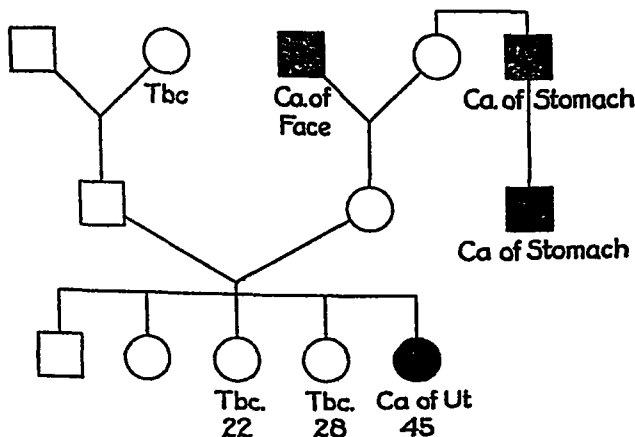


FIG 4 Family history showing association of cancer and tuberculosis

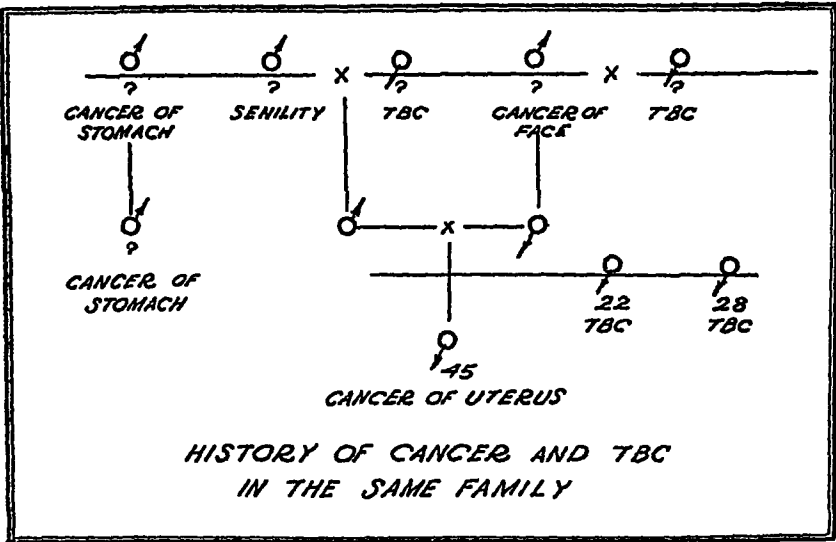


FIG 5. Family history of associated cancer and tuberculosis

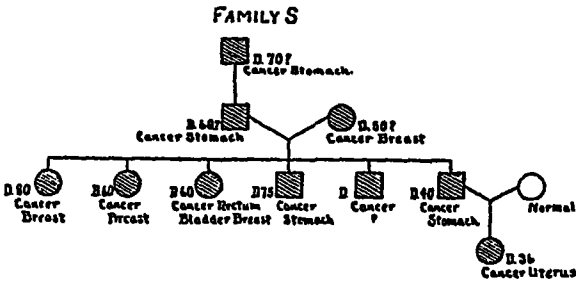


FIG 6. Example of "Durchschlag" inheritance of cancer Also two system predispositions Gastro-intestinal tract and sexual organs

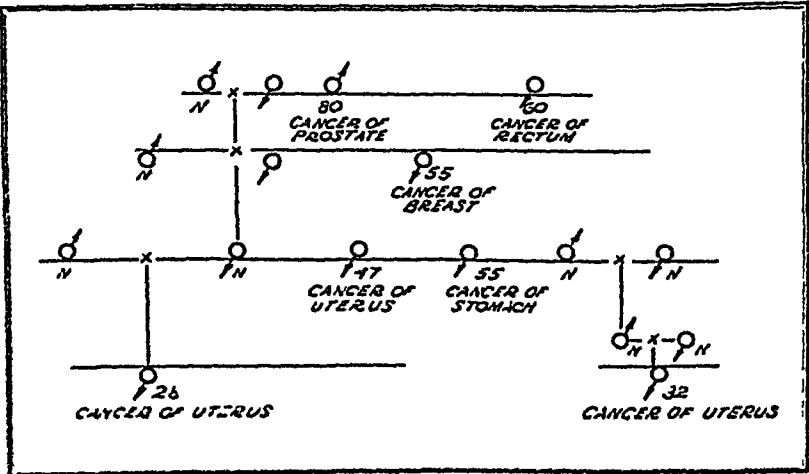


FIG. 7 Example of two system predispositions to cancer Sexual organs and gastro-intestinal tract





died of cancer One son married a woman without any history of family cancer, and their only child died at 36 of cancer of the uterus The other members of the third generation were childless; the family terminated its line with the cancerous great-granddaughter

In all families showing a "Durchschlag" tendency it is important to note the fact that the carcinoma develops at an earlier age in the later generations, so early in some instances that the individual is under the age of 30, a minimal cancer age according to some authorities Apparently there is a progressive inheritance of the carcinoma susceptibility in some members of these families leading to a development of the

carcinoma independently of the action of any extrinsic factor

Others of our histories show very interesting things In some families there is a very marked variation in cancer susceptibility in the different members of the family In Fig 12 is a chart of a family in which for two previous generations the male members died of smoker's cancer of the lip In the present generation there were four sons, three of whom died of smoker's cancer of the lip between the ages of 40-45 The fourth son who did not smoke lived to the age of 63, when he too died of carcinoma of the lip, arising apparently independently of the extrinsic factor This would appear to be a carcinoma wholly intrinsic in nature Fig

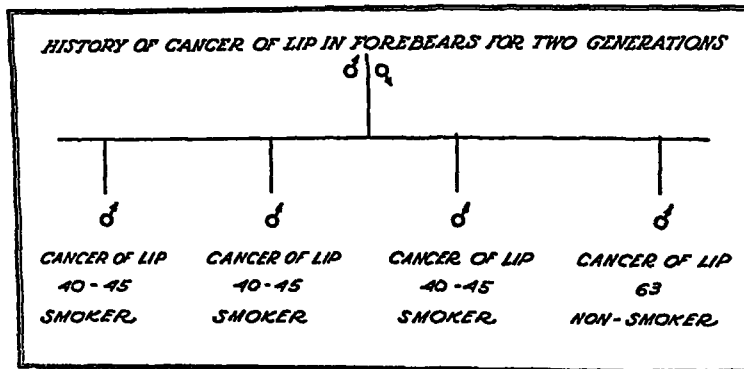


FIG 12 Chart of family showing marked predisposition to "smoker's cancer" in middle life One member, a non-smoker, developed same cancer of lip at 63 years

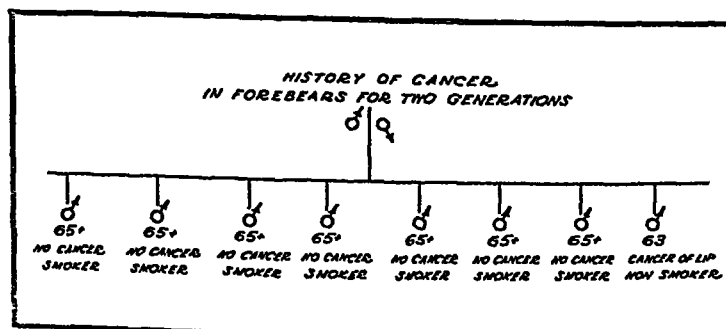


FIG 13 Chart of family with history of "smoker's cancer" for two generations, with seven members of third generation, all smokers, but free from lip cancer, while the eighth, a non-smoker, develops carcinoma of the lip

13 tells a story quite different in its possible interpretation. As in the previous family, the two previous generations showed smoker's cancer of the lip in the male members. In the present generation there were eight sons, seven of whom were smokers and lived over 65 years without developing cancer of the lip, while the eighth son, a non-smoker, died at 63 of cancer of the lip. The cancer-susceptibility which showed in him alone developed purely intrinsically, without the aid of the extrinsic factor. Contradictory as such histories may appear to be on the surface, yet they are also explainable on the grounds of constitutional susceptibility to cancer, and a local predisposition independent of any apparent extrinsic factor.

As to the question of dominance or recessiveness of the carcinoma factor in human families, there would appear to be in some families a dominant inheritance, in others a recessive inheritance of the cancer factor. The great variation in susceptibility found in different members of the same family may possibly be explained by the great complexity of the cancer character. It cannot be a single simple Mendelian character, but may consist of a combination of a large number of factors. Moreover, we are not sure that the inheritance of the cancer-susceptibility in man is always Mendelian. From the available evidence we are sure of two things: a constitutional susceptibility to neoplasm, and a local organ-predisposition to cancer. The first determines that a man may develop cancer; the second determines the organ or tissue involved.

The existence of a constitutional susceptibility to neoplasm and of a lo-

cal organ-predisposition is particularly shown in the case of the gastro-intestinal tract. The studies of Bauer and Aschner, Spiegel, and others, have shown that there is a familial stomach-predisposition showing itself as chronic dyspepsia, particularly of the nervous type, ulcer of the stomach, or gastric cancer. In the study of 255 ulcer patients and 400 normal individuals made by Bauer and Aschner, the incidence of cancer of the stomach in the families of ulcer cases is not greater than 19.83 per cent and not less than 7.63. The minimal value is twice as great as the incidence of gastric cancer in the families of 400 normal controls. Spiegel, in a study of 121 ulcer patients and 200 normal individuals, found that every 6-7th ulcer patient showed carcinoma of the stomach in his family history, while in the non-ulcer individuals only every 40th had a family history of carcinoma. The high incidence of carcinoma of the stomach in the family histories of gastric ulcer cases points to the important rôle played by constitutional organ-predisposition in the origin of gastric ulcer and gastric cancer. When both the constitutional susceptibility to cancer and the local stomach predisposition are present in the same individual, then gastric ulcer may be the local predisposing factor to cancer development. As a matter of fact the development of cancer in a chronic peptic ulcer of stomach or duodenum is but rarely seen; so that if a patient has ulcer he is pretty likely to escape cancer, or is more likely to have it in other parts of the body than in the stomach. In a recent autopsy in my service, a woman with three chronic peptic ulcers of the stomach developed

what is relatively rare in women, a primary carcinoma of the esophagus. It would seem, therefore, that an inferior stomach-constitution in itself does not necessarily predispose to cancer. There must be both a general blastoma susceptibility and a local organ predisposition to cancer present in the individual who develops cancer.

Another important fact in proof of the hereditary nature of cancer susceptibility is the occurrence of symmetrical neoplasms in members of the same family. The slide shows large symmetrical xanthomas of both elbows in two sisters. If our theory is correct that constitutional predisposition and organ predisposition to cancer are necessary to the development of a cancer, we should expect to find in identical twins, examples of neoplasms affecting the same organ and the same part of the same organ. And this is precisely what has been observed in a number of cases. In one case reported by me, malignant teratomas of the ovary developed in each of identical twin sisters. In one case the ovary involved was a mirror image of the ovary affected in the other. We have seen also symmetrical adenofibromas of the breast becoming malignant in identical twins. Symmetrical malignant teratomas of the testes have also been reported in identical male twins. Such occurrences can be

interpreted only as proof of the hereditary nature of cancer susceptibility and local organ predisposition.

Putting all of the observed facts together, as shown by this rapid and incomplete survey, we possess the following data concerning hereditary susceptibility to neoplasm: multiple incidence of neoplasm in family generations, dominant inheritance of neoplasm in some families, recessive inheritance of neoplasm in some families, "Durchschlag" inheritance in some families, appearance of neoplasm at an early age in the later generations, appearance of neoplasm independently of extrinsic factors, multiple incidence of neoplasm affecting the same organ or system, multiple incidence of neoplasm affecting different organs or systems; varying degrees of resistance or susceptibility to neoplasm within the same family generation, symmetrical tumors in different members of the family; and the occurrence of symmetrical neoplasms in the same organ and part of the organ or its mirror image in identical twins.

It seems to the writer that the best interpretation of these facts rests upon the assumption of at least four hereditary factors: the normal constitution resistant to blastoma, the pathologic blastoma constitution, the normal resistant organ or tissue make-up, and

#### FACTS CONCERNING INHERITED NEOPLASM SUSCEPTIBILITY

1. Multiple Incidence of Neoplasm in Family Generations.
2. Dominant Inheritance of Neoplasm in Some Families.
3. Recessive Inheritance of Neoplasm in Some Families.
4. Sex-limited Inheritance of Neoplasm in Some Families.
5. "Durchschlag" Inheritance of Neoplasm in Some Families.
6. Appearance of Neoplasm Independently of Extrinsic Factors.
7. Appearance of Neoplasm at Early Age.
8. Multiple Incidence of Neoplasm Affecting Same Organ or System.
9. Resistance or Non-Susceptibility to Neoplasm in Some Families.
10. Different Degrees of Susceptibility in the Same Family.

FIG 14 Summary of the facts known about inheritance of tumor susceptibility

the pathologic organ predisposition to cancer. Each of these factors must be composite; no one is a simple unit factor in the Mendelian sense. Each one represents large and complex genes in which a hundred or a thousand subsidiary factors may enter and which may mendelize independently or in combination. The old conceptions of dominant and recessive have lost their original significance as far as the inheritance of neoplasm in man is concerned. The possibilities of inheritance in the almost endless combinations that may result, the effect of diluent or intensifying combinations, the occurrence of lethal factors and their combinations, the action of the extrinsic factors of the environment, and other modifying factors make the problem of the inheritance of carcinoma in man one beyond mathematical computation or prediction. The conception of Mendelism which led Maud Slye to regard the inheritable tumor susceptibility as a simple recessive unit character is all too primitive. Characters that show a dominant inheritance in several generations may be so modified that they hereafter show a recessive inheritance. Theoretically the laws of Mendel have added much to our understanding of heredity, but their practical application in human heredity is limited because of the complexity of the problem.

Nevertheless, in some families the four factors mentioned above appear to be inherited as genes. If *B* represents the normal constitution, *b* the blastoma predisposition, *O* the normal organ, and *o* the organ predisposition, the possibilities of the heredity of cancer susceptibility would be expressed in Figs 15, 16, 17, and 18. If *B* is dominant

over *b*, and *O* over *o*, there would be out of nine genetic possibilities, only one cancer candidate, that is, one homozygote recessive *bb oo*, No. 9. But if *b* and *o* are dominant, the individuals, 5, 6, 8, and 9 will be cancer candidates. If *b* is dominant over *B*, and *O* over *o*, only the individuals represented by 6 and 9 would be cancer candidates. The blastoma predisposition of the constitution must be very much more widespread in the community than the number of cancer deaths would indicate because many individuals die before reaching the cancer age. Only in those families in which a definite organ predisposition, *oo*, is present, will the blastoma anlage, *b* or *bb*, assert itself.

The familial occurrence of carcinoma depends in the first place upon the wide distribution of the blastoma constitution, and secondly upon the occurrence of the organ predisposition. If *b* is dominant, then 75 per cent in the first familial generation may expect to be carcinomatous. If *b* is recessive, 100 per cent in the first family generation may show it. If an individual has a father who dies of cancer of the stomach and a mother who dies of cancer of the thyroid, there is no greater chance of the children developing neoplasm than if just one parent has a neoplasm. But should the family history for several generations back show other cases of cancer of the thyroid and of the stomach, then the chances for carcinoma of either thyroid or stomach, or of both organs, are much greater in the progeny. If one parent possesses both pathologic organ predispositions in stomach and thyroid in homozygote form, *bb ss tt*, which may not manifest

## THEORY OF CONSTITUTIONAL CANCER SUSCEPTIBILITY

*B* Normal Constitution

*b* Blastoma Predisposition

*O* Normal Organ

*o* Organ Predisposition

*Hereditary Structure as to Cancer Predisposition Expressed in Usual Formula would be*

*1. BB·OO, 2. BB·Oo, 3 BB·oo, 4. Bb·OO, 5. Bb·Oo, 6. Bb·oo, 7. bb·OO, 8. bb·Oo, 9. bb·oo.*

*If B is dominant over b and O over o, there would be out of the 9 possibilities only 1 Cancer Candidate, the homozygote recessive bb·oo, No. 9.*

*If b and o are dominant the individuals 5, 6, 8 and 9 will be predisposed to cancer since they possess both pathological hereditary factors as heterozygote or homozygote.*

*If b is dominant over B and O over o, only the individuals represented by 6 and 9 would show a cancer predisposition.*

FIG 15

*If 10 per cent of the population die of cancer, the pathologic blastoma-predisposition b must be widely distributed individually; if b is dominant much more than in one-tenth of the population; if recessive more than  $\frac{1}{\sqrt{10}}$  or  $\frac{1}{3.16}$ . In the first case more than every tenth person would possess b, in the second case more than every third would possess it either in simple or heterozygote form. The constitutional blastoma predisposition must be much more extensively distributed than the cancer mortality, since many cancer candidates die of other diseases and escape their constitutional fate. Only in those families in which a definite organ-predisposition oo is present, will the blastoma anlage, b or bb, assert itself.*

FIG 16

*The familial occurrence of carcinoma depends upon the wide distribution of  $b$  in the first place, and secondly upon the occurrence of the organ-predisposition  $oo$ .*

*If  $b$  is dominant:*

$$\begin{array}{rcl} \frac{Bb \cdot oo \times Bb \cdot oo}{BB \cdot oo} & . . . . . & P \\ 2 Bb \cdot oo \} & 75 \text{ per cent.} & . . . F_1 \\ bb \cdot oo \} \end{array}$$

*If  $b$  is recessive:*

$$\begin{array}{rcl} \frac{bb \cdot oo \times bb \cdot oo}{bb \cdot oo} & . . . . . & P \\ & 100 \text{ per cent.} & . . . F_1 \end{array}$$

FIG 17.

*If both parents die of carcinoma of different organs (as stomach cancer,  $ss$ , thyroid cancer,  $tt$ ) the chances for the children are not much worse than in the case of one cancerous parent.*

*Stomach cancer  $\times$  Thyroid cancer*

$$\begin{array}{rcl} \frac{bb \cdot ss \cdot TT \times bb \cdot SS \cdot tt}{bb \cdot Ss \cdot Tt} & . . . . . & P \\ & . . . . . & F_1 \end{array}$$

*If these parents possess no other organ-predisposition, the children would remain cancer-free. If the pathologic organ-predisposition leading to cancer in one parent is present in heterozygote form in the other, 50 per cent of the children would be cancerous. When  $b$  is dominant the number would be reduced to  $\frac{3}{8}$ , 37.50 per cent.*

$$\begin{array}{rcl} \frac{bb \cdot ss \cdot TT \times bb \cdot Ss \cdot tt}{bb \cdot Ss \cdot Tt} & . . . . . & P \\ & . . . . . & F_1 \\ Bb \cdot ss \cdot Tt & (50 \text{ per cent stomach cancer}) \end{array}$$

FIG. 18

itself in the phenotype because he dies of carcinoma of one organ, 100 per cent, relatively 75 per cent, of cancerous children may be expected. The hereditary biologic formula in this case is the same as that of multiple primary carcinoma of different organs.

As to the relation of extrinsic factors to the intrinsic, very little is known. Can an extrinsic factor take the place of the intrinsic organ predisposition, and create a local predisposition? Many workers hold that this is so, but the absence of an intrinsic local predisposing factor cannot be positively proved in any human case. We see, at least, great variations in the potency of the extrinsic factor in the case of different members of the same family. In some, the neoplasm may develop so early in life that the extrinsic factor may be excluded, in some the cancer develops at the cancer age either independently of the extrinsic factor, or dependent upon the latter, other members of the family may reach extreme old age and develop cancer either independently of the extrinsic factor or dependent upon it. Some individuals with intrinsic constitution require an intensive action of the extrinsic factor to bring about the development of cancer.

Some writers on this subject hold that both the constitutional and the local organ predisposition to cancer may be acquired, or one inherited and the other acquired. They explain the occurrence of x-ray cancer, paraffin cancer, arsenic cancer, mineral oil cancers, tar cancers, Bilharzia carcinoma, Kangeri cancer, and carcinomas arising in old scars, as the result of an acquired perversion of regenerative processes. It is not so easy to exclude the exist-

ence of an inherited factor in any of these cases, and the question as to the purely acquired character of the origin of the cancer must still be kept open.

The local organ or tissue predisposition can be recognized in many cases as an embryonal anlage, associated with disturbances of development. To such developmental disturbances we refer the malignant teratomas of ovary and testis, the malignant neuroblastoma of the retina and sympathetic system, the malignant neoplasms of the adrenals and kidneys in the newborn, the malignant hypernephromas and carcinomas of the kidneys in the adult, branchiogenic carcinomas, familial intestinal polyposis, chordoma, angiomas, and numerous others. Cohnheim's theory of tumor etiology has received a new value in recent years, developmental disturbances are the chief morphological evidences of local tumor-predisposition. At least they are the forms recognizable by our present technical methods. In all of these developmental disturbances there is a strong factor of heredity, and some writers dispose of the question of heredity of neoplasm by the assumption that it is the disturbance of development which alone is inherited, and not the susceptibility to cancer. These writers, therefore, hold that carcinoma inheritance is dependent wholly upon the inheritance of malformations or abnormal developmental anlage. This view is not in accord with the actual facts observed. It is true that constitutional and local predisposition to cancer may in themselves be the result of abnormal development, but these writers do not regard it in that sense. Further, may not an inherited tendency to abnormal regeneration in



response to the extrinsic factor be the thing that lies behind the etiology of these supposed acquired forms of cancer?

As far as the practical application of the points brought out in this paper are concerned, the individual who has a single case of cancer developing in two or three generations of his family has not great cause for worry. But the individual who has a family history of the multiple incidence of cancer in several generations should take heed. Particularly important is the investigation of the collateral lines with reference to multiple incidence of cancer, rather than in the line of direct descent. Such an individual with a history of the multiple familial incidence of cancer should avoid all of the known extrinsic agents associated with the etiology of cancer. Chronic irritation of any form that may lead to abnormal regeneration should be removed or obviated. He should not smoke; he should not engage in any industry in which mineral

oil, tar, paraffin, or other irritating products that might lead to the production of cancer, are used. He should not expose himself to irradiation. Scars of the skin, particularly large scars from burns, should be treated by skin grafting. All developmental anomalies should be corrected or removed. Rough pigmented moles should be removed. All chronic inflammatory conditions occurring in such an individual should be healed as quickly as possible.

Finally, there is the question of breeding as a general preventive measure. The man who has a history of the multiple incidence of carcinoma in his family should not marry a woman who has the same kind of a family history, but he should marry a woman who has no history of cancer in her family. It is but rational and logical to apply preventive measures of eugenics to this problem; and till such measures are considered as practical, there can be no great hope for any speedy conquest of this great plague of mankind.

# The Principles of Radiation Treatment\*

By FRANCIS CARTER WOOD, M.D., *New York*

THE relation of bacteria to disease was a mystery until Pasteur and Koch developed culture media which permitted the isolation of the pathogenic from the host of contaminating organisms present in the body and allowed the study of its characteristics in pure culture and facilitated the demonstration on animals of its special qualities. So all broad advances in the understanding of the principles underlying the action of radiation will only be gained by using the same method, that of experiment. Experiment consists only in simplifying conditions of observation so that confusing elements are as far as possible eliminated. The term radiation includes all forms of atomic energy transmissible through a vacuum. The discussion will be confined to a limited region of radiation employed practically, that of the gamma and x-rays, the wave lengths of which are so short that the effects are atomic and not molecular. Ultraviolet light, ordinary visible light, and long wave length heat are therefore excluded from consideration. The study of the biological action of any radiation presumes that we are able to define with considerable accuracy the wave

length of such an agent and its intensity. This is now true for x-rays and the gamma rays of radium, though as yet it has not been possible to measure radium radiation accurately in terms of the international r unit for x-ray.

Assuming these quantitative factors as determinable, it is then necessary to study the action of the rays to learn, if possible, the minute changes in cells or other substances under investigation which follow radiation, and lastly to observe the effect of such changes upon the complex living organism as a whole. At first in order to avoid complications such an organism must be as simple as possible, either a free swimming creature like a protozoon, the eggs of marine animals, like *Arbacia*, the normal habitat of which is sea-water, or minute eggs such as those of the *Ascaris megalocephala*, or insect eggs, of which the most convenient type is that of the fruit-fly, *Drosophila*. The radiation of whole animals or of growing plants introduces so many factors which are not always easy to control that they are not satisfactory for investigations of the laws of biological action. The effects of radiation on considerable amounts of tissue are so complex that their study belongs rather to the clinical aspect of the question and is often a matter purely of statistical observation and does not permit of any unravelling.

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\*Presented in the Symposium on Cancer before the American College of Physicians, Feb 13, 1930

of the finer principles. The difficulty in obtaining approximately normal growth of animal tumor cells or even of normal tissues has prevented the general use of such material in studying the biological effects of radiation.

A. The influence of physical factors upon the biological action of radiation. The first physical factor which has to be investigated in order to observe the biological action of radiation is that of wave length, and those wave lengths are chosen arbitrarily as the regions which are used in practice. This includes all rays whose wave lengths is from 2 angstroms, the so-called long wave length x-rays or the Grenz rays, up to the short waves of radium or mesothorium, many of which lie on the short side of 0.01 angstrom. This limitation excludes the characteristic x-radiation from some of the lighter substances which are largely absorbed in a few centimeters of air, and of course also excludes ultra-violet and other types of light. Within the limits given the wave length of the radiation seems to play no part, provided the measurements are made with an open ionization chamber, using air at the normal temperatures and pressures as the medium ionized. While physically the short wave lengths carry more energy than the long, this is compensated in the chamber by their lack of absorption. The absorption in such a chamber of 10 or 15 cm length is approximately the same as the absorption in the minute biological objects mentioned above. Most physicists and many biologists have long held that it was self-evident that the only effect produced in a cell by radiation is parallel with the absorption of energy;

in other words, that if the absorption in the ionization chamber and the absorption in tissues were the same, the biological results should be the same, and thus the experiments of Wood and Prime and Packard at the Institute of Cancer Research, Columbia University, have shown to be true, for under these conditions of measurement, using a continuous x-ray beam; the biological effects on isolated cells or small aggregates of cells are independent of the wave length. Each cell in the tissues of the human patient must therefore be affected independently of the wave length of the radiation which reaches it. To reach cells deeply placed penetrating wave lengths must be used, for surface tissues longer wave lengths can be used. Whether or not the open ionization chamber measures energy makes no difference in these experiments, because the amount of energy absorbed in the column of air is about the same as that absorbed in the material exposed. In order to parallel the conditions existing both in the chamber and in the radiated tissue, the latter must be of small dimensions and suspended in the air upon thin gauze so that there can be no question of any secondary radiation affecting the amount of x-ray received by the individual cell by "scatter" from surrounding objects. The measurement of the gamma rays of radium cannot be accomplished by an open ionization chamber with any accuracy as yet, so that strictly quantitative comparisons between x-ray and radium have not been made, but the curves of the lethal action of such radiation and also of the Bucky rays exactly superimpose, provided that the 50 per cent. point is used to adjust the

position of the curve on the horizontal axis. The laws governing the lethal action must therefore be the same. The x-ray and radium measurements, however, can be made at present within a moderate percentage error by comparison of erythema doses and by using various measuring chambers, so that the differences can scarcely be more than 10 or 15 per cent. It is therefore probable that when gamma rays can be determined in r units they will be found to be quantitatively equal to the short wave length x-rays, though the final proof has not been brought. But the rate of killing of *Drosophila* eggs is exactly the same with equal quantities of the two radiations as it is with the longer of 2 angstrom units. Hence the sum of the effects of any two wave lengths will be the same as an equal quantity of one wave length, always remembering that this applies to individual cells, and not to large quantities of tissue. The effect on a cell 10 centimeters below the surface of the skin of two half skin erythemas, one with Bucky rays, the other with radium gamma rays will not be the same as if one erythema was given with gamma rays, because much less radiation will reach the cell in the first instance as compared to the last. These results have been confirmed by Holthusen and others on a variety of biological material. Recently Morse and Fricke have shown that the rate of decomposition of hemoglobin and aqueous solutions of ferrous salts was likewise independent of wave length, so that it has been shown that this law is true of animal tumors, of *Drosophila* eggs, and of solutions. The discordant results which have been published by Russ, Dognon

and other workers are probably due to some error in technique. Thus the old statement of Kronig and Friedrich, published in 1918, is confirmed, though it has been pointed out that their results were only accidentally correct, because the dimensions of the ionization chamber which they used happened to give measurements which were independent of the wave lengths used.

B. The influence of the time and quantity relationships of radiation are not so fully determined. Wood and Prime showed that on animal tumors a threshold existed with radium below which no biological effect took place, in other words, the cells could repair the damage as rapidly as they were injured. Packard has shown that the same is true of *Drosophila* eggs with x-ray. But above this point Kronig and Friedrich demonstrated that no difference could be observed when the dose was diminished by one-fifth and given over five times the time, in other words, the product of the intensity by the time was a constant. Hence within certain time limits biologic material can be employed to measure the intensity of radiation. Wood and Prime showed this also for tumor particles with x-ray and radium at ratios of one to eight, and Packard has shown that the law holds with *Drosophila* eggs, but it is difficult with all this experimental material to extend the time factor much more than one to eight, as most of the tissues used cannot be preserved for more than four or five hours without undergoing such deterioration as to interfere with the accuracy of the test. Further studies which have been made are chiefly those of Regaud and his colleagues, which have been made upon

the testicles of rams They showed that long-continued small doses are more effective than short high intensity doses. But in these experiments there were complications brought in by the very complexity of the reactions which they regarded as indicating their endpoint The same is true of the radiation of plants or of tumors growing in the host. It is not possible to eliminate completely the interplay of other factors which may increase or diminish the effectiveness of the radiation. The general feeling, however, from the clinical point of view is that the prolongation of radiation over a very considerable time permits more effective treatment with less damage to the normal tissues than a large dose given in a short time Certain animal tumor experiments carried out under Regaud's auspices point in this direction also, but the work needs to be rechecked with a large number of different tumors before it is safe to make any generalizations

C The physical and chemical actions which underlie the biological effects of radiation —The nature of the physical actions which take place in tissues when they are rayed by short wave lengths can only be guessed at at the present time The passage of such radiation through the tissues may be assumed to set free electrons but this assumption is based wholly upon the demonstration by Wilson of the freeing of such electrons in a gas by x-rays or gamma rays and rendering them visible by the condensation of moisture upon them during their flight. The instantaneous photographs show that the velocity of an electron increases with decreasing wave length, and that such secondary electrons occasionally strike

other atoms and set up secondary radiations either of the same wave length, of a slightly smaller wave length, or a very much longer wave length, the latter being due to the production of the characteristic radiations of elements of low atomic weight The demonstration of these very long wave lengths has been obtained by photographing their spectra in a vacuum as they are completely absorbed by air. The atom is also capable of scattering rays of the same wave length as the impinging beam and also rays of longer wave lengths. (The Compton effect.) Each of these different types of rays is capable of giving rise to fresh electrons. The assumption is generally made that the action of radiation is due to such electrons. It is certain that a pure electron beam may cause the death of cells This was first shown by Exner many years ago, who exposed cells to a beam of electrons deflected from a radium source by means of an electro-magnet. Recent experiments which have followed the development by Coolidge of a tube which gives a beam of electrons in the open air have shown the highly destructive effects on tissues of such electron showers Penetration of course is very slight because these electrons themselves are stopped by a few inches of air. Whether the radiation itself has any direct effect is doubtful, for even in studying the photographic effect of gamma or short wave length x-rays the experiments lead to the belief that it is an electron phenomenon in the silver halide which makes the image developable The effect of such short wave length radiation cannot be referred to direct heat for the amount of heat set free by a beam of x-rays is so small

that it can be scarcely measured. Dessauer has suggested, however, that active molecular actions may be set up either by the rays or by the stopping of electrons and that these vibrations are equivalent to an enormous quantity of heat set free at one point, and that this heat may, for example, start small coagulation centers in the protein molecule. An attempt has been made by one of Dessauer's pupils to demonstrate such points of coagulation by studying protein solutions with a dark field illuminator, and it has been observed that there is an increase in the number of small visible particles in such a solution after radiation, but after longer exposure the number decreased again. The experiment must be tried on inorganic colloids in which coagulation can not take place before this result can be accepted as sustaining Dessauer's viewpoint. It is possible also that the setting free of electrons changes the electrical charge of the atoms of the tissue, and this induces chemical changes. It is certain that the action of intense radiation over a long time will decompose water, setting free hydrogen, and that such an effect might result in damage to the protein molecule, but as yet this is all pure speculation. In a gross sense protein solutions can be so altered that they coagulate easily, changes have been observed in the viscosity of protein solutions after radiation, and various protein suspensions have revealed visible precipitation after prolonged exposure. The radiation of hemoglobin produces also alteration in the molecule of that substance. The surface tension of serum is altered by heavy radiation, and its reaction is changed toward the acid side. Lipoids

are also altered. But all of these results are obtained only with enormous doses of radiation, hundreds of times those required to kill living cells, and while they suggest processes which may go on in such a cell, they do not prove that such alterations underlie the lethal action.

One of the most interesting phenomena has been observed on the eggs of *Arbacia* and protozoa, that the permeability of the cell membrane, as tested by vital stains, is greatly increased by very moderate exposures, and that as the cell regenerates and regains its original condition, the absorbed dye is again extruded.

*The latent period*—The raying of dead tissue reveals no morphological changes. Living cells show no immediate change, even after considerable radiation. This latent period varies a good deal with the biological material and with the dose, the larger the dose, the shorter the latent period. As previously stated, a threshold dose is always necessary to produce noticeable changes. The cells can regenerate after a certain amount of exposure and apparently return to a perfectly normal condition. When the dose exceeds this threshold and after a considerable period, scarcely ever less than 24 hours, morphological changes begin to make their appearance. They are noticed chiefly in the nuclei, in the form of breaking up of chromosomes into fine, dust-like particles, obliteration of the nuclear membrane, and swelling of the cell, which appears glassy, and ultimately in the formation of syncytial masses. These are all familiar to those who study tumors after radiation. Cinti has photographed these changes

the nucleus and ultimately causing the death of the cell by such damage, does not interfere with the metabolism of carbohydrates sufficiently to stop the muscular contractions

The radiation of cancer and also normal material in culture often requires large doses to accomplish the lethal effect. If such cells are immediately transplanted to fresh media after radiation they may continue to grow under a suitable dosage. If left in the medium for a suitable time they will not grow. This can be interpreted in two ways, one that there is some toxic substance generated in the medium either by the direct action of the radiation or by the excretion of metabolic products from the injured cells. The other is that such cells can "make the grade" only if supplied with fresh food. The same is observable with animal tumors. If they are radiated and immediately transplanted, growth will take place. If they are left for a considerable time before grafting, no tumor results. This is easily explicable on the basis that not only were the radiation effects developing in the cells under conditions which do not permit of regeneration, but that the grafting process causes additional trauma, and that the cells when they are grafted are not capable of obtaining sufficient nourishment to enable them to go on and grow. The assumption has been made that the tissues elaborate toxic substances after radiation which destroy the cells, but there are two experiments which make this very doubtful. The first was reported by Jürckow who rayed the chest of a patient under a grid-like filter, so that an area of 2 or 3 mm. was exposed to

radiation, and a similar adjacent area received no radiation. The tumor receded only in the exposed strips, showing that this hypothetical tissue reaction did not extend even a couple of millimeters. The second experiment was that of Wood, who showed that the dose required to destroy the tumor cells was the same, whether the tumor was rayed in the animal, or exposed *in vitro* and then inoculated. That the circulation contains a cell poison after radiation is negated by transfusion experiments from rayed animals to those bearing tumors. No effect is produced.

*Immunity to radiation*—The action of the rays has also been supposed to cause the tumor cells to become resistant, a so-called radiation immunity. The observation is unquestionable, as tumors which have been rayed for a long time cannot be as effectively treated by renewed radiation as those which have never been exposed. Here again other factors appear. One of the effects of radiation, and an extremely important one, is damage to the terminal arterioles. This consists of swelling of the endothelium, of edema and vacuolization of the sub-intimal tissues, and of the muscular coats, so that the vessel in exceptional circumstances may be completely closed or be filled by a thrombus. This obviously cuts off food from the tumor cells, and causes the clinical appearance of the destruction of the growth. When the cells start to grow again, it is impossible to give to such damaged tissues the same amount of radiation, because they are badly nourished. The vessels having once been closed, no clinical effect can be obtained by radiation, for there is no longer any means of diminishing the blood supply

to the growing cancer cells. That any change occurs in the tumor cells themselves owing to repeated radiations has been disproved by Prime, who rayed a highly virulent animal tumor and then transplanted it. This process was repeated many times, and at the termination of the experiment, no difference in the lethal dose of radiation was found as compared to an unrayed tumor. The same is true after raying the tumor in the animal with sublethal doses, then comparing the killing dose with that of previously unrayed tumors. It is evident that a simpler explanation than that of some immunity must be sought. The one given above seems to be the most probable.

*Sensitivity to radiation*—The sensitivity of tissues, both *in vitro* and *in vivo*, varies considerably. The resistance of the brain cells to heavy radiation has already been mentioned. Endothelium and the walls of the vessels are much more sensitive. The tissues of the bone marrow are extremely sensitive. On the other hand, radiation of the circulating blood shows that the blood cells are resistant after they have once reached their development. Certain of the connective tissues resist successfully enormous quantities of radiation. The tissues of the kidney and adrenal are rather sensitive. What underlies these biological differences is impossible to state at the present time. Wood and Prime have shown that different animal tumors of similar types require different dosages, and the same observation was later made upon human tumors. The morphology of the tissues is not necessarily a guide to their radiosensitivity. One tumor may be sensitive, whereas a tumor of exactly the



same morphology may be resistant. Such biological phenomena escape our analysis at the present moment.

### CONCLUSIONS

I. The action of radiation is in all probability due to the secondary effect of free electrons released by the action of the rays on the atomic structures of the tissues

II. The effect on the individual cell is independent of the wave length.

III The effect on large masses of tissues is dependent on the wave length in that the intensity of the radiation at any given depth is a function of the

wave length and the scattering of the rays in the tissues.

IV. The effect is twofold, primarily a direct one on the cells, and a secondary nutritional damage due to vascular injury. No proof is yet available of a tissue toxicity as a factor in cell destruction

V. There is no evidence of a cellular immunity following radiation

VI Cells vary greatly in their sensitivity to radiation for reasons as yet unknown

VII The ultimate evaluation of the therapeutic possibilities of radiation rests on clinical observation.

# Spontaneous Pneumothorax\*

## A Discussion of Its Causes

By FRANK J. HIRSCHBOECK, *The Duluth Clinic, Duluth, Minn.*

**B**Y "spontaneous pneumothorax" I mean to indicate all pneumothoraces which are not induced by external factors, either accidental or for therapeutic purposes. In the literature one finds that some writers limit the term spontaneous pneumothorax to those instances in which the etiology is not demonstrable by our clinical examination, but I believe that these might be more properly classified as the idiopathic type of spontaneous pneumothorax in order to avoid confusion. The distinction in classifying this group separately is of importance, because of certain specific characteristics in the idiopathic cases.

Spontaneous pneumothorax occurs most often between the ages of 15 to 45; according to Nikolsky<sup>1</sup> in 80 per cent of the cases. Males are affected more often than females, in the proportion of 4 to 1. This is usually explained on the basis of increased effort and strain in the male. It is said to occur with equal frequency on both sides of the chest, though individual statistics vary on this point.

Spontaneous pneumothorax may be multilocular or unilocular, depending on pleural limitation; partial or total;

unilateral or bilateral; simple or complicated with effusion, and may be recurrent. In the bilateral cases, of which about 15 have been reported in the literature, death does not necessarily ensue, as one might surmise, as 4 of the series have recovered.

Spontaneous pneumothorax has also been classified clinically into certain types. The pneumothoracic cavity may be of the closed type, meaning thereby a sealing up of the communication between the pleural cavity and the pulmonary tissue; open, if a free communication exists between the pleura and the pulmonary fistula; or of the valvular type if a check-valve action is developed, either because of the valvular nature of the opening or because of a fibrinous flap. As a result on inspiration air more or less freely enters the pleural cavity, but is not effectively expelled during expiration, resulting in a gradual increase in the intrathoracic pressure on the affected side, usually with the development of serious dyspnea, cyanosis, mediastinal shifting and circulatory embarrassment. These latter symptoms serve to distinguish the more serious valvular type from the others but the diagnosis of this type can be further established by the introduction of a needle connected with the manom-

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eter tube of a pneumothorax apparatus. It is observed that in the closed type the manometric pressure decreases with inspiration and increases with expiration; in the open type the manometric reading remains at zero, whereas in the valvular type the positive pressure is greatly increased and may be as high as 10 to 14+ instead of the normal -2 to -5

It has long been known that pulmonary tuberculosis is the most frequent cause of spontaneous pneumothorax, but that it is an almost universal cause, as is oftentimes intimated, must be denied

The most elaborate statistics on the etiology available in the literature up to the present time are those often quoted from Biach<sup>2</sup>, based on 38 years' experience in 3 Vienna hospitals. It was found that in his series of 918 cases, 715 were due to pulmonary tuberculosis—an average of 77 per cent. The next most frequent cause was gangrene of the lung, with 65 instances, many of which were probably associated with pneumonia, empyema rupturing into the lung with 45 cases, and injury with 32. Other causes of lesser importance and frequency were rupture of the lung from bronchiectasis, pulmonary abscess, emphysema, infarction, paracene-

usually estimated that about 10 per cent of all fatal cases of pulmonary tuberculosis have had a spontaneous pneumothorax at some time during the course, and that the complication develops in about 2 per cent of all cases. In tuberculosis it develops much more frequently in the cases that have softening than in those with a fibrous indurative type of disease. Pneumonia is a relatively more frequent cause in childhood. About 40 per cent of the total cases in children are of tuberculous origin according to West<sup>3</sup>, but Stoloff<sup>4</sup> points out that in 35 per cent of the cases a non-tuberculosis pneumonia is the cause. All clinicians of extensive experience have seen pneumothorax develop as a result of empyema rupturing into the pulmonary tissue, inducing thereby a pyopneumothorax.

In generalized emphysema, pneumothorax rarely occurs, Saussier<sup>5</sup> reporting its occurrence five times in 131 cases. Stahlein<sup>6</sup> thinks that it does not cause more than 1 per cent of the total. Its development in generalized emphysema is rare, but of serious prognostic importance, because of the existent disease in the lungs and its subsequent deteriorating effect upon the heart. Kahn<sup>7</sup>, and Emerson and Beeler<sup>8</sup> have reported its occurrence in chronic asthmatics.

In my discussion I wish to emphasize particularly the so-called "idiopathic spontaneous pneumothorax," which evidently occurs relatively frequently, as the reports in the literature would indicate. In these no definite etiological agent can be uncovered from the history or the examination. These attacks come on suddenly, as a rule, with a rather dramatic symptoms in the

way of pain or local chest discomfort, and with a varying degree of shortness of breath. They tend to run a favorable course, going on to spontaneous recovery in a few weeks, with re-expansion of the affected lung and no vestigial objective effects. They are distinct from the other types in that they are rarely accompanied by effusion and exhibit no marked constitutional symptoms. This aids greatly in differentiating them from the far more serious tuberculous type. The good prognosis and the rarity of opportunities for necropsies have made it difficult to establish the pathological factors which may induce the condition. Because these cases are clinically so unlike the usual tuberculous cases, with the latter's tendency to exudation, constitutional symptoms and serious prognosis, many writers, particularly LeWald<sup>9</sup>, have sought to establish this condition as a definite specific clinical entity distinct from tuberculous causation. At the time of Dr. LeWald's presentation, a discussion by Drs. Miller, Willy Meyer and Lemon expressed the belief that they were probably always primarily tuberculous. Many isolated pathological postmortem findings tend to support this belief in a large measure. Two such patients with idiopathic spontaneous pneumothorax were examined with a thoracoscope at a meeting of the Swedish tuberculosis physicians, and in 1 a crater-like ulcer was found on the lung and in another a contracted scar, presumptively tuberculous. Kleeman<sup>10</sup> reported 2 cases that revealed tuberculosis, 4 and 7 years later respectively, and Haves reports a similar instance. LeTulle reports a case of spontaneous rupture with a single tuberculous nod-

ule, and West and Flint report a similar rupture of minute tuberculous foci. These instances are truly tuberculous. A pneumothorax originating at the site of a Ghon's primary node probably is an extreme rarity.

Of great interest has been Orth's<sup>11</sup> finding of a ruptured localized emphysematous bleb in an apex of the lung at postmortem examination. Fischer<sup>12</sup> reports three such cases, and Schoenfeldt one. In Pitts<sup>13</sup> case a ruptured emphysematous bleb was found with a torn adhesion near it. Tearing of a pleural adhesion is probably rarely a cause of spontaneous pneumothorax per se. Instances have, however, been reported, notably by Cahn and Brunner<sup>14</sup>, in which the ruptured emphysematous bleb was in close proximity to a pleural adhesion. Mönckeberg actually found a bleb on the edge of an adhesion. It is quite evident, therefore, that many instances find their origin in the rupture of a localized emphysematous vesicle somewhere in the lung, probably more commonly in the apex than elsewhere. Insofar as these emphysematous blebs may be due to previous tuberculosis, presently inactive, we may consider the condition as "paratuberculous," but I do not believe that tuberculosis is the sole factor in the production of these emphysematous vesicles. Ljungdahl<sup>15</sup> reports 2 instances in which rupture occurred a short time after an acute pleurisy. Two of my cases likewise followed such an event, and I do not believe that acute pleurisy can be assumed as being necessarily tuberculous in the absence of any effusion. It may be rheumatic or of a non-specific type. The most exhaustive study of the relationship between the

emphysematous blebs and spontaneous pneumothorax was made by Hayashi<sup>16</sup> in Fischer's laboratory, who in 1914 studied 77 cases. Three were due to a rupture of a localized emphysema in the apices, with evidence of a localized tuberculous fibrosis in the apex and pleural adhesions. He also found 4 other instances in which the bullae had not ruptured. They were found to empty with difficulty, but filled easily on inspiration, leading to gradual enlargement. This is in accord with the experimental work of Coryllos and Birnbaum<sup>17</sup> and the clinical observation of Jackson, Lucker and Lee<sup>18</sup>, that incomplete obstruction tends to lead to the development of emphysema. Hayashi points out that a primary apical induration as the result of a tuberculosis may induce a localized bulla and yet be entirely inactive otherwise from the standpoint of tuberculous activity.

I believe it may be assumed, therefore, that the idiopathic spontaneous pneumothoraces develop most commonly from emphysematous bullae, localized in character, their formation induced by fibrosis and induration in their proximity, and that these may be tuberculous or not. In the apex they undoubtedly are. The clinical course indicates that they are at variance with the usual tuberculous process.

#### CASE I

##### *A Patient With Left Sided Total Pneumothorax of Eleven Years' Duration, Probably Tuberculous in Origin*

J. Z., male, 41 years of age

Family history negative to tuberculosis and no history of any contact with the disease. A physician in 1919 advised him that he had a dextrocardia while attending him for influenza. Attended again because of an acute respiratory infection in October, 1929, another physician advised him at that time also that he had a dextrocardia. After the latter illness an x-ray picture was taken and it was observed that the patient had a total pneumothorax of the left side with extreme displacement of the mediastinum and its contents to the right. The roentgenogram (Fig. 1) also showed an apparent old tuberculous process on the right side and a calcified pleural area on the side of the pneumothorax. The patient denies knowledge of any illness except as stated. The patient has been employed in moderately heavy manual labor.

On examination he has the general appearance of vigor. His heart is distinctly displaced to the right side and might be mistakenly assumed to be dextrocardia. The roentgenogram, however, indicates the true condition. Examination otherwise was negative except for the usual physical signs associated with a pneumothorax. The vital capacity was 1700.

*Comment.* This case is of interest because of the long duration of a pneumothorax, namely 11 years, with a strong presumptive evidence of its having been primarily tuberculosis, but never positively proved. The absence of effusion would indicate that no active tuberculosis process was present. The type of pneumothorax is either open or valvular. Bittendorf<sup>19</sup> reports a case of 25 years' duration as indicated by the history. Wiles<sup>20</sup> had an instance with a duration of 20 years. It would appear that ordinary manual labor is not inconsistent with a permanent total pneumothorax on one side.

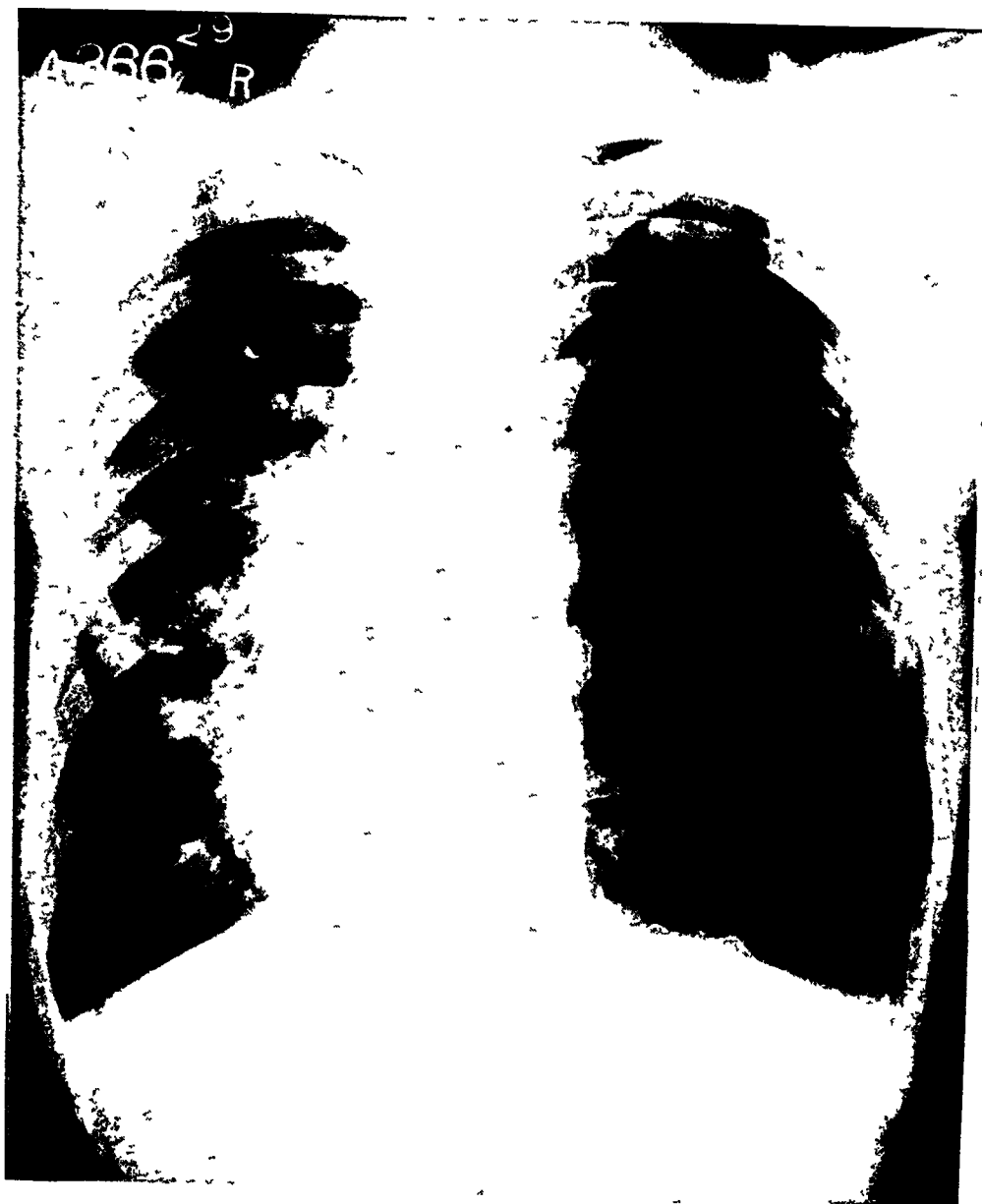


FIG 1—Case 1 Spontaneous pneumothorax of eleven years duration with displacement of heart to right side—probably primarily tuberculosis

## CASE II

*A Patient With a Bilateral Pneumothorax Due to a Contusion of the Chest Without External Evidence of Injury or Fracture of the Bones Comprising the Thoracic Skeletal Wall*

G J, male, 11 years of age, injured July 11, 1929, in an automobile accident, sustaining a simple fracture of the left thigh, with slight general bruising. There was considerable respiratory distress and cyanosis and the patient died 4 hours after the injury.

The x-ray picture (Fig 2) revealed a pneumothorax on both sides, on the right side with a positive pressure, probably due to a valvular pneumothorax. Both lungs showed laceration of the lung tissue. Careful examination of the bones comprising the chest showed no evidence of any fracture, but an extreme compressibility of the thorax.

*Comment* This is a case of bilateral pneumothorax due to an injury, without any external evidence or any fracture of the bones in the chest. It is of interest chiefly because of the difference in pressure in the two sides of the chest in spite of the bilateral nature of the condition, the right side showing a marked increase in positive pressure. This would indicate that there was no communication between the two pleural cavities through the mediastinum.

patient had a partial pneumothorax on the right side with a slight effusion in the right costo-diaphragmatic angle, and with a definite succussion wave on moving the patient.

In ten days the lung had expanded and the effusion had absorbed.

The patient was seen the day after the onset of her symptoms. She had slight pain in the right chest, which was coincident with the first day of her menstruation. It was observed later, during subsequent attacks, on January 10, 1928, August 8, 1928, September 29, 1928, March 4, 1929, April 5, 1929, and May 28, 1929, that the attacks always recurred on the right side and were exactly similar in the partial nature of the pneumothorax and the slight effusion in the right base, with healing and disappearance of the effusion in 10 to 14 days. These attacks were always associated with the menstrual period.

The patient is no longer under direct observation, but states that she still has attacks of a similar nature, but probably not quite so severe, since the last time she was observed in May, 1929.

*Comment* There is nothing about this patient's history to indicate tuberculosis as more than a possibility. The history of an acute pleurisy may or may not be related to the symptoms ensuing 2 years later. The pleurisy may have been rheumatic in type in view of the paternal history and the patient's history of having had tonsillitis. The peculiarity of the recurrences lies in the association with the menstrual period. This association is difficult to explain, unless we may assume that there is aberrant ovarian tissue under the pleura which ruptures from time to time, leading to a partial pneumothorax and exudation.

## CASE IV



FIG 2—Case 2 Bilateral pneumothorax, following chest injury without fracture of bones comprising thoracic wall

Positive pressure on right side with shifting of heart to left Note pneumothorax on left, as well



S. N., male, aged 24, single, first examined March 15, 1926, because of a pain in the left chest.

Examination revealed a friction rub in the left base.

The diagnosis of acute pleurisy was made.

The family history and personal history indicated nothing suggesting the possibility of tuberculosis, and the patient had always been in good health except for diseased tonsils.

On April 10, 1926, the patient returned with a history of having had a severe sharp pain in the left chest four days previous, unassociated with effort, and examination revealed a total pneumothorax on the left side (Fig. 3).

On May 21, 1926, all symptoms had disappeared, and the x-ray examination indicated a return to the normal without the development of any complications in the interim.

A few days later the patient returned with friction sounds throughout the left side of his chest, but no subjective symptoms except for a slight feeling of heaviness. A few days later these signs had disappeared.

#### CASE V

M. G., male, aged 32, single. Patient first seen at the office July 20, 1929, because of a sudden severe pain in the right chest, coming on without effort.

The family history indicated that one brother had died of tuberculous meningitis, but aside from this there was no history of tuberculosis in the family otherwise.

Personal history. The patient had had typhoid fever as a child, recurring attacks of tonsillitis, and a duodenal ulcer.

Examination. The physical examination on July 20, 1929, including the roentgenogram (Fig. 4) revealed a partial pneumothorax on the right side, and in the right base evidence of diaphragmatic pleural adhesions.

On August 12, 1929, all subjective and objective symptoms had disappeared, and the lung had re-expanded.

*Comment.* Aside from the fact that in Case V there was a history of tuberculous meningitis in the brother, there is nothing about the personal history of these patients or that of their family

otherwise which would indicate tuberculosis as a factor. The adhesions in the right base in Case V would indicate some old pleuritic disease. The rapid recovery, without complications, places these two cases into the group of idiopathic spontaneous pneumothorax. No positive etiology could be discovered.

#### CASE VI

*A Patient Whose Necropsy Revealed Localized Bullous Emphysema in the Right Apex Due to Fibrosis and Induration in Its Proximity. No Pleural Adhesions Were Present. No Evidence of Spontaneous Pneumothorax.*

J. S., male, 50, widower.

Family history. Wife died of tuberculosis in 1921, and one of his children also since that time of the same disease.

Personal history. The patient himself had an operation for a hypernephroma in April, 1923. Metastases had developed to the left antrum in 1929, and the patient entered the hospital in September, 1929, for relief from the malignant condition in the superior maxilla. The patient later died as the result of his metastasis and a terminal pneumonia. The autopsy incidentally revealed two small localized emphysematous bullae in the right apex (Fig. 5) in proximity to an area of fibrous induration, evidently primarily tuberculosis.

*Comment.* This case is illustrative of the fact that localized bullous emphysema occurs in the apex in association with disease in its proximity. These may occur without any clinical or roentgenographic evidence of disease. Rupture of such bullae when it does occur leads to pneumothorax, and might be considered clinically as idiopathic, and not related to tuberculosis, in the absence of pathological data.

#### CASE VII

*A Patient With a Very Large Bullous Emphysema in the Middle Lobe of the Right Lung, Evidently Developing to Enormous*

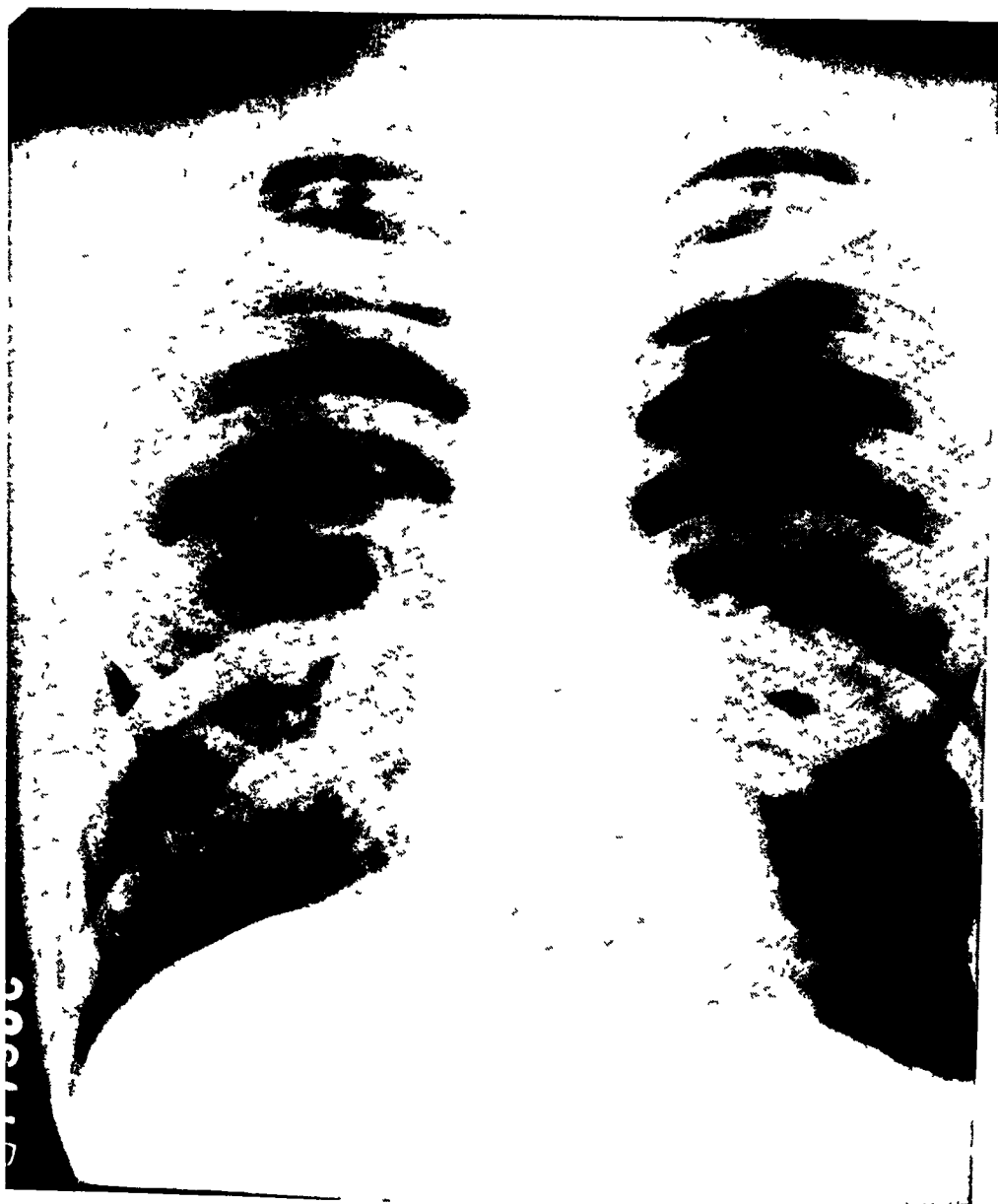


FIG 3—Case 4 Complete pneumothorax on left side of idiopathic type

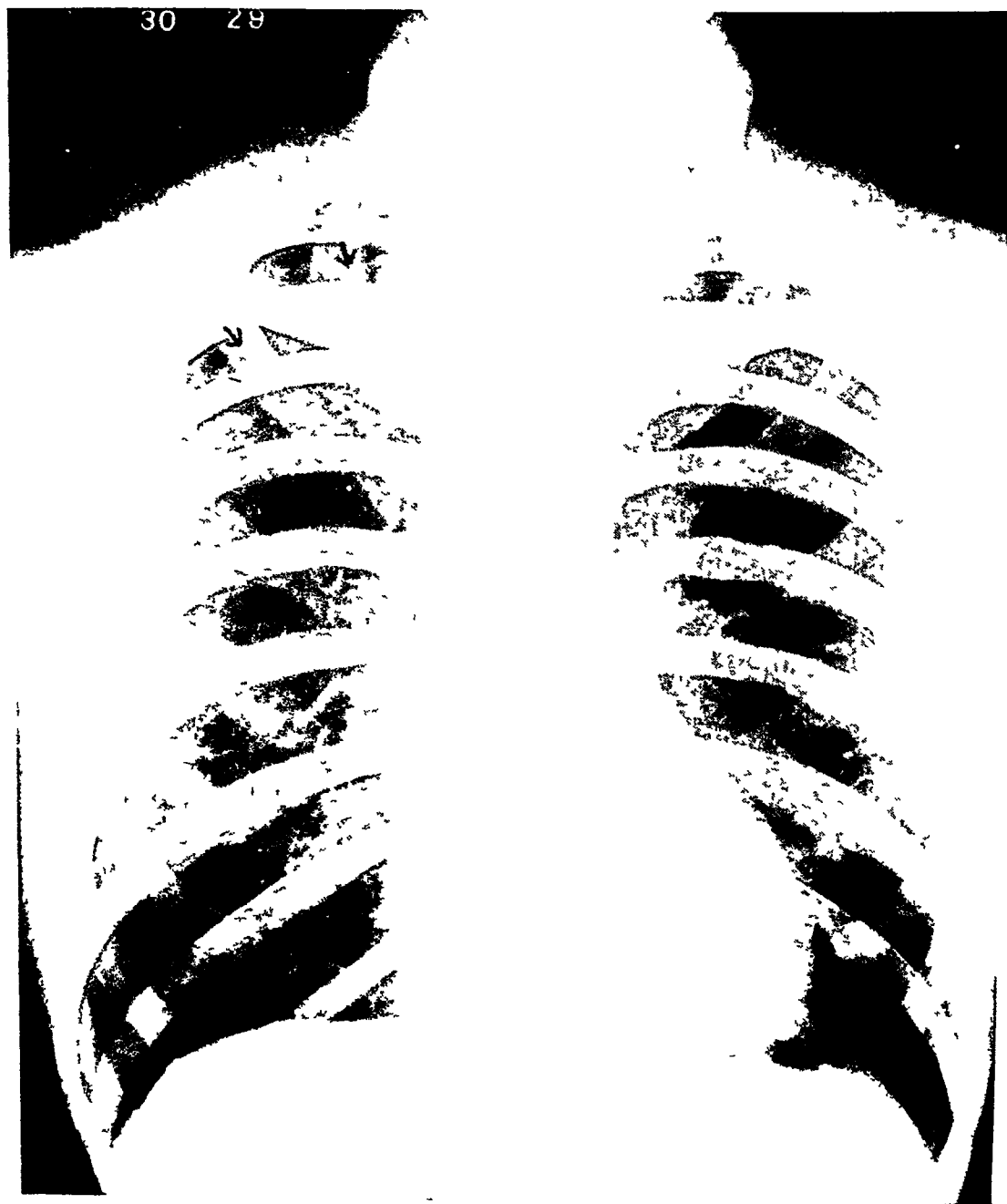


FIG 4—Case 5 Partial pneumothorax on right side—idiopathic or primarily tuberculous  
The only suggestion of tuberculosis was the history of tuberculous meningitis in a brother



FIG 5—Case 6 Photograph of the apex (only) of the right lung with several unruptured emphysematous blebs. These blebs when ruptured are probably the usual cause of idiopathic spontaneous pneumothorax.

*Proportions Within 30 Days, Death Ensuing Without the Development of a Pneumothorax*

S. M., male, 46 years of age, first seen August 15, 1927, with classical symptoms of Graves' disease, and a metabolic rate of 50+.

Prepared for operation with Lugol's solution, and thyroidectomy performed on September 3, 1927, when his condition was satisfactorily stabilized. He left the hospital September 14, 1927, after an excellent, uneventful recovery. A roentgenogram taken September 8, 1927, was negative.

On October 31, 1927, the patient returned, with a history of acute illness for three weeks prior to his admittance to the hospital. The patient had a diastolic and systolic murmur, scattered areas of bronchopneumonia, and a right pleural effusion (Fig 6).

On November 2, 1927, a quart of clear fluid was removed from the right pleural cavity. The patient died the next day.

Necropsy revealed a bacterial endocarditis of the aortic and mitral valves, infarction of the spleen and kidneys. The lungs showed adhesions near the apex on both sides, and several large bullous emphysematous areas (Fig 7) along the anterior surface of both lungs, one on the anterior portion of the right middle lobe the size of a foetal head. The pleural cavity on the right

side contained one quart of clear fluid. Bronchopneumonic patches were evident throughout both lungs.

*Comment* This case would indicate that an enormous bullous emphysema may develop in a short period of time—in this case certainly within 1 month. Tuberculosis was not a factor in its production. Any pulmonary condition, acute or chronic, which does not permit of the emptying of a certain lung area, but does permit filling with air, leads to emphysema. This is in accord with the experimental work of Coryllos and Birnbaum<sup>17</sup>, (Fig 8) who found that a valvular obstruction leads to emphysema in the parts tributary to the obstruction.

#### CASE VIII

*A Patient With a Massive Saccular Emphysema Filling the Right Chest Cavity, With Increased Intrasaccular Pressure, But Without Rupture Into the Pleural Cavity*

R. G., male, 21 months of age.

Family history negative. Father and mother living and well. No other children in the family.



FIG. 6. Case 7. A large emphysematous bulla in the lower right lung field with pneumonia above (Necropsy report).  
It had developed rapidly at about one month's time without rupture and pneumothorax.



FIG 7—Case 7 Photograph of right lung removed at necropsy of Case 7 Note large emphysematous bulla of recent development in lower half of photograph This had not ruptured before death

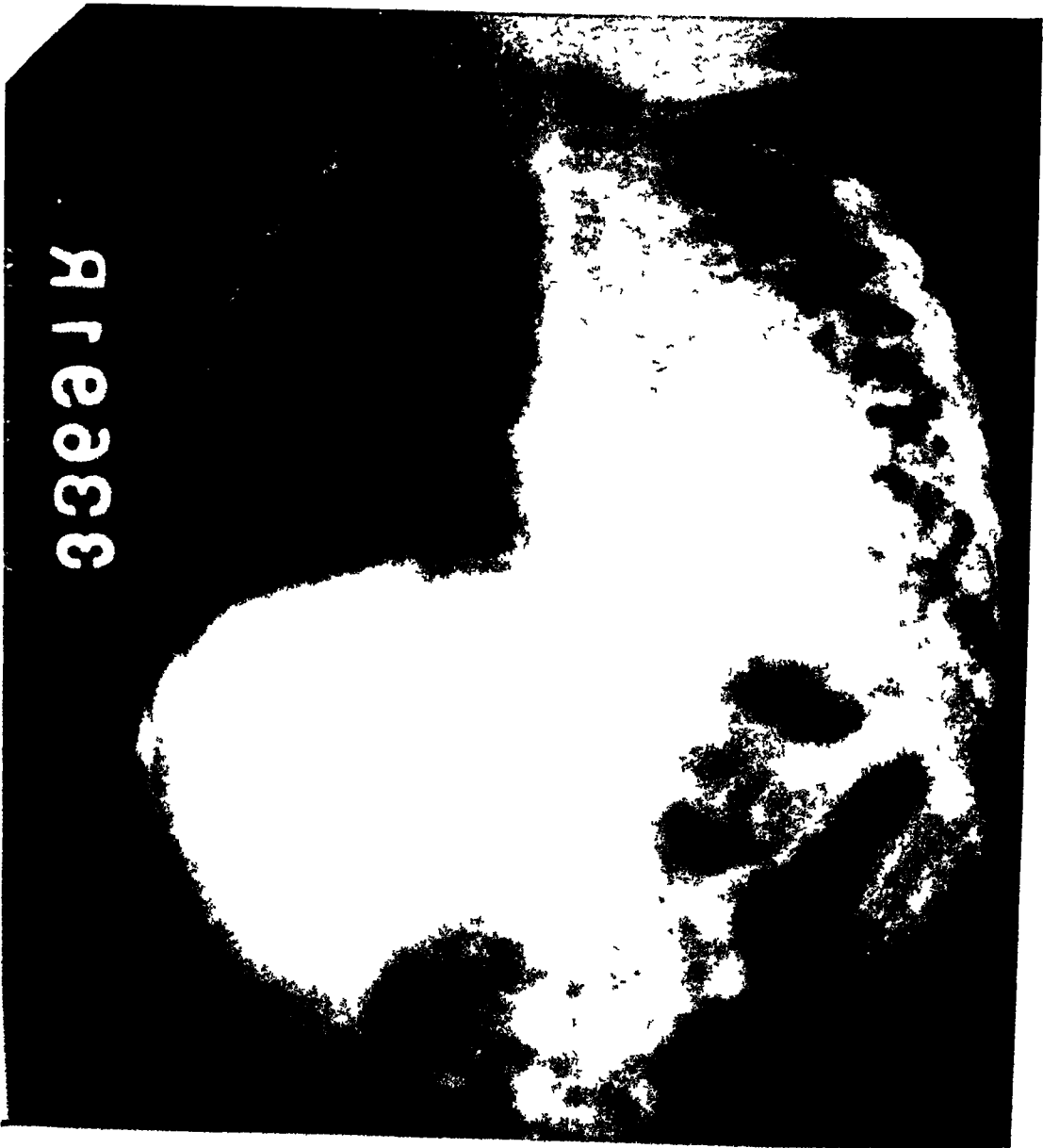


Fig. 5. Foreign body partially obstructing main left bronchus in a child illustrating diffuse emphysema resulting therefrom. (See text)

Past illnesses Child was full term Birth weight 7 lbs, 4 oz Measles at 8 months, but never ill otherwise Breast fed for 6 months

First examined April 9, 1928 Gave a history of having been ill for 5 days with a slight fever, without a cold or cough, and in an improved and convalescent condition apparently, but with a history of having lost 7 ounces in the past week

On examination it was observed that the breath sounds were entirely absent in the right lung, but present on the left, with an extreme hyperresonance on percussion The hands and feet were a trifle cold, possibly from lack of circulatory vigor X-ray picture taken of the chest (Fig 9) indicated an enormous spontaneous pneumothorax with increased pressure The Von Pirquet and Mantoux were negative Blood counts normal, white blood count 14,000, differential normal

Since that time the patient has been under observation, without any material change in the condition In May an attempt was made to reduce the positive pressure by the introduction of a needle, but because of the onset of discomfort in breathing and a cough the effort was discontinued after about 300 cubic inches of air were removed An x-ray picture taken immediately thereafter showed the outline of a large emphysematous shell in the right chest (Fig 10) Subsequent consultation elsewhere led to a diagnosis of lung cyst, but I believe that the diagnosis of a saccular emphysema is more in accord with the objective findings Within the past few months several efforts have been made at reducing the intrasaccular tension by the introduction of a needle, and at one time a response was effected with a partial inflation of the lung so that it was visible to the right of the spine in the roentgenogram The intrathoracic pressure, however, increased, and the lung shadow to the right was again effaced with the displacement of the mediastinal contents to the opposite side The child's condition at the present time is unchanged

*Comment* This child evidently has a large massive saccular emphysema of the right lung, with a marked increase in the intrasaccular pressure, resulting

in a collapse of the remaining tissue of the right lung, so that it is quite invisible on the roentgenogram The manner of origin of this emphysematous sac is difficult to understand as the history does not supply any data on this point

#### SUMMARY

1 Spontaneous pneumothorax is any pneumothorax which develops aside from external causes Idiopathic spontaneous pneumothorax is that rather frequent type in which clinically no cause is demonstrable Idiopathic spontaneous pneumothorax has a favorable course, unattended by serious symptoms or complications, as a rule, and tends to heal in a few weeks, with no residual findings

2 The cause of idiopathic spontaneous pneumothorax from a necrotic standpoint is difficult to establish because of the rarity of necropsy findings, but it would appear that localized emphysematous blebs are the most frequent cause

3 These localized emphysematous blebs may be the result of indurative processes in the subpleural pulmonary tissue, regardless of primary origin, or of emphysematous processes in the proximity of adhesions It is doubtful if pleural adhesions are, per se, a frequent cause

4 Tuberculosis is probably the most frequent primary cause Any condition leading to the formation of emphysematous bullae may be likewise a factor

5 Instances of idiopathic spontaneous pneumothorax are cited, and certain instances of saccular emphysemata of varying size, unassociated with pneumothorax, reported



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# General Management of Pulmonary Tuberculosis\*

By ERNEST S. MARIETTE, M.D., *Oak Terrace, Minnesota*

THE presentation of a paper on such a subject to this group would be like "carrying coals to Newcastle" were it not for the wide difference of opinion among sanatorium physicians regarding the use of rest which, of course, forms the backbone of the sanatorium treatment of tuberculosis. We glibly tell the patient that sanatorium treatment offers him his best chance for recovery. But what do we mean by sanatorium treatment and does it mean the same thing to all physicians? Nearly all physicians agree that it means bed rest during the acute febrile stages but there is not the same unanimity of opinion regarding the use of rest after the acute phase has passed and the long period of convalescence has begun. Some believe that merely keeping the physical activity below the fatigue level is all that is necessary during this period. Others believe that bed rest should be continued long past the period when the pulse and temperature have become normal, even possibly until fibrosis has ceased. Such a wide difference of opinion concerning the use of rest indicates that an analysis of the

basic principles underlying its use is warranted.

What rest means to the various physicians depends upon what each physician expects to accomplish through its use. This in turn depends upon the extent to which he believes that rest can influence the mechanism of recovery, as it is revealed in Koch's phenomenon. Von Pirquet called this phenomenon allergy, indicating broadly a condition of altered reactivity. As he used the term allergy included both the acute inflammatory and the immunological phases of this altered reaction. The exact relationship of these phases to each other and their significance in tuberculosis are not yet determined. Without attempting to settle the controversy, this discussion will consider them as separate yet related and co-existing apparently antagonistic reactions. Allergy is now limited to the acute inflammatory phase of the altered reaction which, because of the acuteness of the response, is a source of danger to the host. This phase of the reaction is due to tissue hypersensitivity and accounts for much of the symptomatology of tuberculosis. Immunity is now limited to that increase in resistance which tends to protect the host against tuberculosis by retarding the growth and limiting the spread of

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tubercle bacilli. Just how this is accomplished is not known but it is represented in part at least by an increase in the ability of the body to form fibrosis which prevents the circulatory exchange between the tubercle and the body. This phase of the reaction is responsible for whatever tolerance the body may develop towards tuberculosis.

From innumerable experimental studies, Kjaer has concluded that tuberculosis represents a general infection rather than a local one with a rather frequent moving about of bacilli, resulting in a few visible foci, may be only one, and several concealed ones, all more or less held in check by the relative immunity which develops as a result of the first infection. He believes that this gives us a picture of tuberculous infection somewhat similar to that of syphilis with its microorganisms rather widely distributed before its focus of inoculation comes to light.

Tuberculous infection, however, causes no symptoms until allergy develops. Then the symptoms vary from those of slight moment to those of great severity depending upon the degree of allergy present and the resistance of the body, as both are modified by the number and virulence of the bacilli and the frequency of implantation. If the allergic reaction is so intense as to overcome the immunological reaction, fatal tuberculosis may result. If on the other hand the resistance or immunity is greater than the inflammatory reaction, the symptoms subside but the bacilli and may continue even to the lungs and appear. Both of the processes may take place in the same individual and the result may be a chronic infection or a severe one.

plates. Because the immunity which develops is only relative and never complete, there is always the danger that healing will not be firm and sound before a new focalization occurs and the process begins over again.

Fortunately for most of us, the infection of tuberculosis is usually moderate, calling forth a rather slight allergic reaction with mild general symptoms and with a rather high degree of relative immunity and with a long enough time between periods of focalization for that immunity to become so well established that clinical disease does not develop. Sometimes, however, something happens such as acute illness, over-fatigue, massive infection, or the unusual "stresses of environment" to upset the delicate balance between allergy and immunity and allergy again arises and all of the previously, partially healed lesions become active again and clinical tuberculosis ensues.

There are certain factors in bodily growth which should also be discussed in the consideration of any outline for the general management of tuberculosis. The first is the marked atrophic changes which take place in the lymphatic system shortly after the advent of puberty and which continue throughout life. The second factor is that the ability of the body to form fibrosis increases from birth until old age. One cannot but wonder whether these growth factors influence, through a modification of allergy and immunity, the type of tuberculosis which develops before and after puberty. Theoretically both immunity and allergy should be greater in childhood than in later life but the effect of the processes of immu-

Therefore, the bacilli should be fixed where they lodge, i.e. in the tissues, more promptly and the acute manifestations of tuberculosis should be more marked in childhood than in adult life. But childhood tuberculosis is essentially a lymphatic disease rather than a tissue disease and is usually benign but with tremendous possibilities for future damage. Adult tuberculosis on the other hand is essentially a tissue disease and constitutes most of our clinical tuberculosis. If these growth factors do influence, to some extent at least, the type of tuberculosis which develops before and after puberty, then the mode of living required to control tuberculosis might be modified according to age. The child requires much less strict supervision as regards rest than does the young adult.

No reason need be given this group why the lungs are involved in the tuberculosis process more frequently than any other organ of the body. Attention, however, should be called to the fact that tuberculosis can develop in any other organ of the body. When it does, it is usually the result of a metastatic infection from a pulmonary focus. Because of this, the general management of tuberculosis should include a thorough search for foci in any organ of the body and a plan of treatment that will include both the local and general conditions.

All of these factors of allergy and immunity, of infection, of growth and of metastasis enter into our picture of chronic fibroid tuberculosis. In its changing allergic state and in the variations in resistance are to be found the explanation of the relapses and remissions so common in chronic tuberculo-

sis. It is for this type of disease and based upon these phenomena that we are attempting to outline a new mode of living.

The foundation for this new mode of living is rest which alone of all of the cures advocated for tuberculosis has stood the test of time. In the past rest was used in the treatment of tuberculosis as it was in other diseases, that is, only while there were symptoms of toxemia or for a short time after the symptoms had disappeared. Then it was discontinued and supervised exercise so regulated as to keep the patient's physical activities below the fatigue level was begun. Relapses occurring under this treatment which was adequate for the other diseases, were considered unavoidable, due to the nature of the disease, or "to the will of Allah." When we began to take serial x-ray plates we were better able to correlate our cases clinically with what was discovered at the autopsy table. Thus we learned that subsidence of symptoms meant not a cure as it did in the other diseases but merely that the acute inflammatory process, which is due to the circulatory exchange between the body and the tubercle, was quieting down and that the cure as represented by fibrosis or encapsulation, upon which the prevention of this circulatory exchange depends, was just beginning. Further study gave visible proof of two facts, first, that the formation of fibrosis was enhanced by rest and retarded by exercise just as the union of broken bones is enhanced by rest and retarded by constant motion. Second, that relapses due to pulmonary strain were much more likely to occur while fibrosis was forming than after encap-

sulation had become complete. This indicated that our former failures might not be due "to the will of Allah" but to treatment which permitted increased pulmonary strain before the healing was strong enough to stand it. The resulting conclusion was that if bed rest, which reduces pulmonary movement to a minimum consistent with living, and, which had brought about a subsidence of symptoms and the beginning of the immunological response had been continued until that response had ceased, encapsulation might have been more complete and relapses less frequent.

In preparing the following standards for the use of rest in the treatment of tuberculosis our sole motivating idea has been the restoration of the patient to the status of a wage earner in the shortest possible time consistent with a fair degree of certainty that his recovery will be as permanent as possible, thus reducing the frequency of relapses. We believe that this result can be best secured by one long term admission rather than by several short term admissions.

Sanatorium is put on bed rest, which means that he must remain in bed twenty-four hours a day. The only exceptions to this rule are certain "repeaters" and elderly people and old chronic fibroid cases where the problem is more of a public health than a medical one, and certain cases of doubtful diagnosis where all of the evidence at hand points to a non-tuberculous condition or a case of non-clinical tuberculosis. The reason for the use of bed rest during the period of toxemia and possibly for a short time afterwards is apparent to all. The advisability of the use of rest for the non-toxic patient is not so universally accepted. However, as the recovery for the non-toxic patient as well as for the toxic patient depends upon how complete the fibrosis is and as fibrosis forms more rapidly and more completely under conditions of rest than it does under conditions of even modified exercise, it follows that the atoxic patient needs bed rest and is greatly benefited thereby. Also, absence of symptoms and a sense of apparent well-being causes the average atoxic patient to minimize the significance of

the symptoms, and the progress of the patient as it is revealed in serial x-ray plates at intervals of two to three months. In general the teen age group and young adults need much more intensive rest than does the child or older adult. A "sloppy" caseous lesion needs much more intensive rest than does a chronic fibroid lesion. Bed rest need not be so intensive after the symptoms of toxemia have disappeared, the patient's general condition has returned to normal and the lesion is progressing satisfactorily from an x-ray point of view.

Because of these variables we have attempted to provide certain standards governing the type of case and condition of the patient in each group.

In doing so we realize fully that such rigid standards will be unbearable for some and concessions will have to be made. Obviously it is better for such people to read, to sit up in bed or even to go to the bathroom than to lie fighting restraint like a caged animal. What we have tried to do is to establish an ideal with the understanding that it may have to be modified at times.

TABLE I  
CLASSIFICATION OF BED REST  
*Glen Lake Sanatorium*

ACTIVITIES	INTENSIVE (1)	STRICT (2)	REGULAR (3)
Sit up in bed for meals and other purposes	No	No	Yes
Meals	May or may not feed himself lying on side after food has been cut	Feed himself lying on side	Feed himself sitting up
To x-ray, lamp or treatment room	Only in the bed	Only in the bed or on a litter	In wheel chair
Occupational therapy, reading, writing, etc	No O T work No writing Certain cases may read if bookrest is used	Yes, while on side or lying down	Yes, sitting up in bed
Type of disease	Toxic—febrile Caseous non-febrile Certain far advanced cavity cases that are non-operable receive prolonged intense bed rest	Non-toxic fibro-caseous lesion. More extensive fibroid lesion. Patients in group (1) who have improved sufficiently to stand more freedom in bed	Non-toxic fibroid lesion. Long standing lesion of any degree group (1) and (2) because of sufficient improvement

It is impossible to state definitely just how long a patient is held at each step. Dependent upon the factors mentioned above, i.e. the age, the extent and character of the lesion, the symptomatology and what is happening to the lesion as determined by x-ray pictures repeated every few months, the patient is either held in a position of status quo or is advanced to the next step.

We have divided bed rest into three groups (1) intensive bed rest, (2) strict bed rest, and (3) regular bed rest

(1) *Intensive bed rest* The patient spends the entire twenty-four hours as quietly as possible. He is not allowed to read, write or to sit up in bed but may or may not feed himself after the food has been cut up. The acute febrile case and the young adult belong in this group

(2) *Strict bed rest* About the only difference between this group and the former is that a limited amount of reading and writing and occupational therapy work may be done. In general, the patients in this group are those with a non-toxic fibro-caseous lesion or more extensive fibroid lesion or those patients in Group 1 who have improved sufficiently to warrant a slight amount of mental activity

result expected from bed rest has been obtained. That involves, of course, the question, what is the desired result? Is it merely a subsidence of symptoms and a quiescence of the disease or as complete an investment of the tuberculous process as the immunological response can produce? If the latter condition is the desired one, then no change should be made in the treatment as long as fibrosis is going on. The standard which the surgeon applies in the treatment of bone and joint tuberculosis, namely, fixation until ankylosis and healing ceases, applies just as aptly in tuberculosis of the lungs and should be used in pulmonary disease. Furthermore, there is general agreement that pneumothorax which produces a much more complete rest of the diseased lung than does bed rest, should be carried out for at least three or four years. If such rigid standards are necessary

stereoscopic x-ray plates until the symptoms of toxemia have disappeared and the body has made good its deficit. Our experience in this has borne out Stewart's conclusion that if six months rest in bed has had some effect on the frame and figure and symptomatology of the patient, maybe another six months in bed will have the like effect upon the tuberculous lesion.

Admittedly there are cases which will improve and even heal enough for resumption of ordinary life without such rigid treatment. As yet we have no test *but the trial and error method* for determining the unusual resistance which such individuals must possess and hence no index but that for making an exception of these cases. If that method is tried and the case proves to be one of *only* usual resistance, the results may be exceedingly disastrous. So the safest plan is to use bed rest even longer than absolutely necessary for in the words of Trudeau, "I know I have hurt nobody by rest but I am quite sure I often have by allowing them to exercise." Pratt in advising prolonged bed rest writes in 1918, "It takes a long time for scar tissue to form, hence according to the extent and the severity of the disease months and years must elapse after the development of a fresh tuberculous process before pulmonary exercise can be undertaken without danger."

V B #3924—Min (a) Single

Admission—Temperature range first three weeks—97 to 99.6° (rectal)

Pulse range first three weeks—68 to 92 with two jumps to 106 and 108

Weight 137½

Sputum examination negative but guinea pig inoculated with specimen of sputum developed tuberculosis

8-19-29—Entrance x-ray Fibroid pc lesion 2nd I S L and thickening of right interlobar pleura

Two subsequent x-rays showed clearing

Next x-ray 7 months after admission shows no change so patient allowed to go to bathroom

8 months after admission patient is still going to the bathroom

Weight 145#

G S #3384—Male, White, M A (b) Single

Admission—Temperature range first twelve days was 98 to 99.4° (rectal)

Pulse range—68 to 86

Weight 135#

Sputum—Gaffky IV

Previous history—Well until June, 1927, when he had the "flu" from which he did not seem to recover. By August he had developed a dry cough and had lost 10 pounds. His physician told him he was anemic. His condition did not improve and in September his physician told him that he had inactive tuberculosis.

In February, 1928, he developed pleurisy with fever and in the latter part of March a consultant diagnosed tuberculosis and he was sent to the Sanatorium.

Entrance examination—+ on right. Left negative, checked by three consultants.

Entrance x-ray—Dense fibroid pc infiltration right apex

Hazy pc infiltration in left 1st and 2nd I S

After fifth month sputum became negative and has been negative since. Weight 175#

Subsequent x-ray shows continuous improvement until that one taken 13 months after admission. This shows no improvement so patient is allowed to go to the bathroom.

Next x-ray shows improvement so patient remains in status quo

19 months after admission x-ray shows apparently stationary lesion so patient started to meals

Exercise begun—20½ months after admission

22 months—x-ray—no change—exercise increased



These two cases illustrate the difference in the length of time bed rest may be used in a minimal case and a moderately advanced case. Both show excellent symptomatic and anatomic results, as shown by clearing and fibrosis as seen on the x-ray plates.

The fourth question is, what will happen to the patient's morale during such a period of prolonged bed rest? We admit that such a period of prolonged bed rest may possibly weaken the morale of the patient so that he becomes hospitalized. Therefore, when the progress is satisfactory, we believe that mental exercise should be gradually increased while the patient is still observing physical rest. This may even include a course of vocational rehabilitation, instructive reading and occupational therapy carried out under medical supervision. This will keep his mind active so that he is better able, upon his discharge, to adjust himself to the new environment of the working world than he would have been otherwise. In planning this, one should never forget that mental exercise is exercise and may be as injurious as physical exertion.

After healing has ceased under the use of bed rest and the process has become stationary, as determined by x-ray pictures, another type of treatment is necessary. What this is will depend upon the extent of the healing. If slight, then dependent upon the type of lesion, i. e. old chronic fibroid, fibro-caseous or caseous, exercise or collapse therapy is indicated. If marked, and nearly complete, then exercise so carefully regulated as to promote further healing rather than to interfere with it is indicated. This can best be accomplished by using the same standard for increasing exercise as was used in determining when bed rest should be discontinued and exercise begun. That is, "while the patient is improving no change in the treatment is indicated." So, if fibrosis, which has become stationary under rest begins again under a certain amount of exercise, say, on going to the bathroom or to the dining room or on one-half hour or more exercise, then this amount of exercise should be continued until fibrosis or favorable pathological activity ceases. When it does, of course, exercise

the continuation of fibrosis. Guiding a patient through such a period requires an understanding of tuberculosis infection, the pathological response of the body to its presence and the resulting symptomatology, both local and systemic. The chief systemic symptoms are those represented by chronic fatigue, unstable temperature and pulse and indefinite gastro-intestinal disturbances.

Because of certain factors of growth previously mentioned, the limitation of the activities of the teen age and young adult group should be greater than for any other age of life.

Nothing has been said so far about the question of food and fresh air in the treatment of tuberculosis. We believe that a diet adequate in calories, vitamins and minerals for the man in health is suitable for the consumptive. In the past, the value of fresh air has been over-emphasized. The body can receive all the stimulation it needs in a well ventilated room, so constructed that it is not too warm in summer and with enough radiation in winter to keep the day temperature at about 65° and the night temperature about 40°.

## CONCLUSIONS

In outlining the general management of pulmonary tuberculosis one should consider all of the factors, infection, allergy and immunity, growth and metastasis and should so plan the treatment that the acute inflammatory symptoms can be controlled and that the formation of fibrosis will not be interfered with but will be enhanced. This can best be accomplished by adhering to the maxim that as long as fibrosis is forming no change in the treatment is necessary. If the improvement under rest has been marked, then exercise carefully controlled is necessary. If on the other hand, the disease shows little or no improvement after a few months rest in bed then, dependent upon the type and condition of the lesion, either exercise or some form of collapse therapy is indicated.

Note. Under the plan of general management as outlined above, 33.9 per cent of our pulmonary cases now in residence have had or are now receiving some type of collapse therapy.

The results obtained under this plan in 1929 as compared with those of 1925 when we began to follow this outline are very interesting.

## CONDITION ON DISCHARGE

	Improved or Better Than Improved		Unimproved or Dead	
	1925	1929	1925	1929
Far-advanced	20%	42.5%	80%	57.5%
Moderately advanced	63%	83.2%	37%	16.8%
Minimal	86%	89%	14%	11%
Extra-pulmonary	85%	94.8%	15%	5.2%
Childhood	95%	95.8%	5%	4.2%

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# Myxedema Heart With Report of One Case

By JAY C. DAVIS, M.D.,

*University of Minnesota and Minneapolis General Hospital, Minneapolis*

**M**YXEDEMA heart is now a recognized clinical entity. In the last few years cases have been reported from various parts of the world. I have been able to collect 21 authentic cases from the literature with telorontgenograms and electrocardiograms revealing the condition of the heart before and after thyroid therapy.

The slides shown here are from a previously unreported case now on the medical service at the Minneapolis General Hospital. I am greatly indebted to Dr. G. Fahr, Chief of the Medical Service, for the privilege of reporting this case. The patient is a female, 48 years of age, with a history of myxedema of over eight years duration.

On admittance to the hospital six months ago, June 21, 1929, because of frequent, burning urination due to a urethritis, she presented a typical myxedema. She had the broad expressionless face of myxedema, the skin was a sallow color, thickened, in folds, dry and scaling. The scalp was dry and in places the hair was thinned out. She had a disinterested stare. There was marked mental retardation and slow muscular movements. She was deaf and her memory was very poor. She gave a history of dyspnea on exertion for the past five years. Cyanosis of the lips was present and on examina-

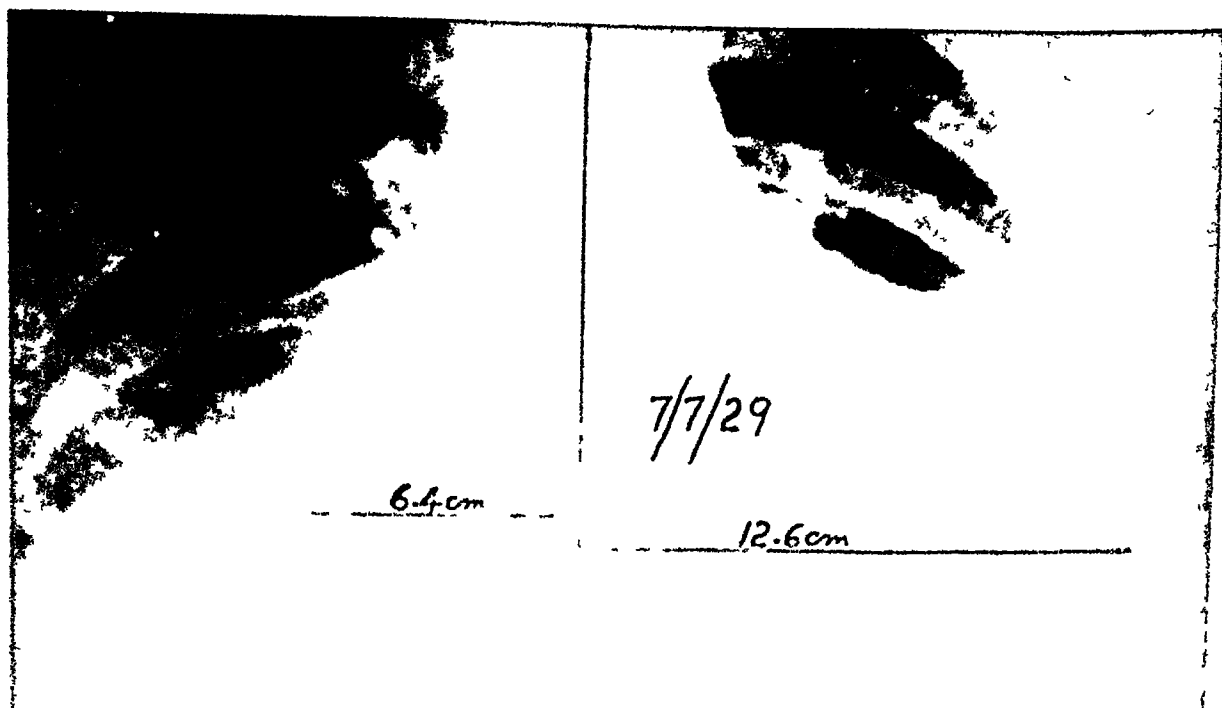
tion there was found marked generalized cardiac enlargement, a systolic murmur at the apex, a liver palpable one finger below the costal margin in the midclavicular line, râles in the lung bases and a pitting edema over the lower extremities and sacrum. The temperature, pulse and respirations were normal. Blood pressure was 115/60. Basal metabolic rate was  $-27\%$ .

At this time the blood was normal. The urine showed a faint trace of albumin, occasional red cells, a few pus cells. Free hydrochloric acid was absent from the stomach after histamine.

At this time a six foot heart plate revealed a transverse diameter of 19 cm. The enlargement seemed to involve all chambers of the heart. The electrocardiogram showed very low T waves, PR 0.2. She received 24 cc of Tincture Digitalis (1 cc =  $1\frac{1}{4}$  cat units) in the next 14 days without change in the size of the heart. Digitalis was now stopped and she received 50 grains of Armour's thyroid extract in 17 days with a resultant decrease in size of the heart to 13.9 cm which means a reduction of 5 cm in the transverse diameter. The electrocardiogram returned to normal. The change in the patient was remarkable, she lost 21 pounds in weight, became active mentally and

physically and took great pride in helping with the ward work. The cyanosis, dyspnea, palpable liver, râles in the lung bases, and pitting edema had all disappeared. Her vital capacity rose from 1700 to 2200. At the end of 7 weeks she had received 175 grains of thyroid and the transverse diameter of the heart was 12.8 cm. The electrocardiogram was normal. Basal metabolic rate +15%. Thyroid was now stopped. The heart began to dilate and in 4 months had dilated to a transverse diameter of 17 cm. The electrocardiogram showed a return to the abnormal findings present on admission, namely iso-electric T waves, PR interval of 0.2. All this time the patient was kept

doing approximately the same amount of work. All her former symptoms and signs of cardiac decompensation began to return, the basal rate dropped to —32%. Under the fluoroscope scarcely any movement of the cardiac borders could be seen. All of her former symptoms of myxedema returned; she became very sluggish, mentally and physically, and gained six pounds in weight. She no longer wanted to help around the wards and complaining of the cold was given a bed in one corner of the ward where she could keep all windows closed. Thyroid medication was resumed on February 11, 1930, and we do not have the slightest doubt but that in a few weeks she will be bright and



cheerful with a normal sized heart and a disappearance of all the present signs of cardiac decompensation

Myxedema heart was first described by Zondek<sup>1</sup> in 1918 when he reported four cases from Kause's clinic in Berlin. At that time he described generalized heart enlargement, normal blood pressure, slow pulse rate and electrocardiographic changes. Under the fluoroscope the heart appeared very sluggish in its movements. He noted low or absent P waves, absent T waves and changes in the QRS complexes. On thyroid his heart underwent changes similar to the present case. The first cases reported in this country were those of Dr. G. Fahr<sup>2,3</sup> in 1925 and 1927. He not only reduced the hearts

to normal size, but caused them to dilate again on withdrawal of thyroid.

All of the cases of myxedema heart seen in Dr. Fahr's clinic have had P waves on the electrocardiogram. Most of his cases have had negative T waves in one or more leads, abnormal QRS complexes and abnormal PR intervals, all of which have returned to normal on thyroid medication. Three of his cases had a negative QRS in lead 3 which returned to normal on thyroid. The present case developed a negative QRS in lead 3 on thyroid and returned to normal when the heart dilated due to withdrawal of the thyroid extract.

There have been cases reported of enlarged hearts in myxedema that do not decrease in size on thyroid, al-

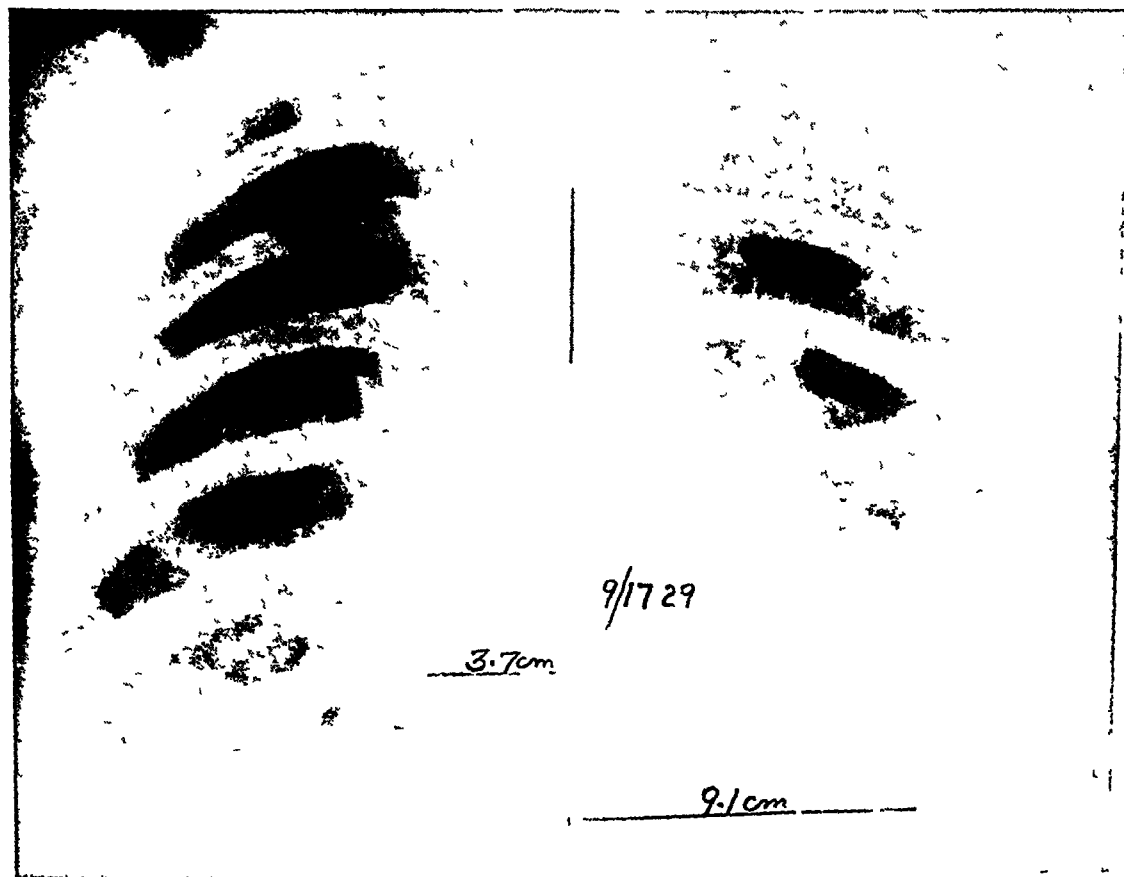
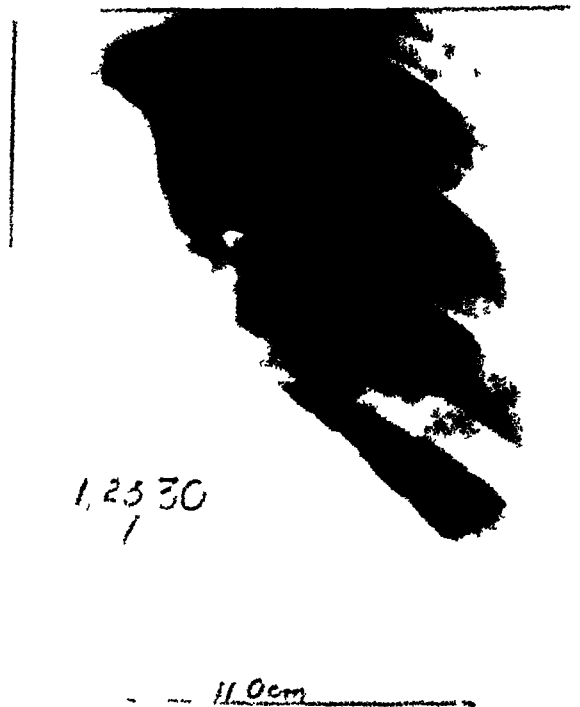
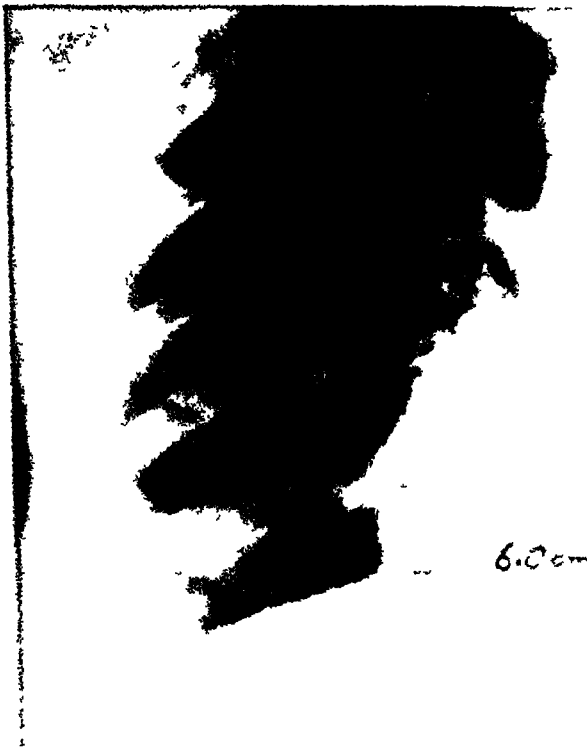


FIG. 2 Six foot plate taken 9/17/29 showing reduction in size of heart after thyroid therapy

though the symptoms of myxedema disappeared.<sup>4</sup> There are several possibilities here, either the enlarged heart was due to some other cause such as coronary disease or hypertension, or they were not given a sufficiently long time to return to normal. At this clinic it has never been claimed that all myxedemas have myxedema heart any more than one would say that all myxedemas have secondary anemia and nephrosis, nor that it was not possible for an enlarged heart from another cause to coexist with myxedema. Some of our cases have taken two to three times as long as others to return to normal size.

Another result that may be observed is a return to normal of the size of the heart and still not have any marked change in the electrocardiogram. Likewise the patient may have anginal attacks which disappear on thyroid,<sup>5</sup> while others continue to have anginal attacks and a few develop the pain after thyroid medication. Herrick<sup>6</sup> of Chicago, Baron<sup>7</sup> of Minneapolis, and others have noted anginal attacks in people with marked anemias who showed changes in their electrocardiograms. When the blood returned to normal, the attacks of angina ceased, and the abnormalities of the electrocardiogram disappeared. One of Fahr's



cases showed electrocardiographic evidence of coronary disease which disappeared after thyroid but reappeared six months later and has remained ever since. This is not unexplainable when we consider the following:

It is impossible to predict whether a case will have angina pectoris before or after thyroid therapy and whether it will disappear, remain, or develop after

thyroid medication. The thickness of the walls of the coronary arteries, the amount of control over the size of the coronary lumen through the vagus nerve, the degree of anemia present, the rise or fall of blood pressure, the length of systole, and the velocity of blood flow are all factors that must be considered in these cases. It should not be surprising that a patient with myxe-

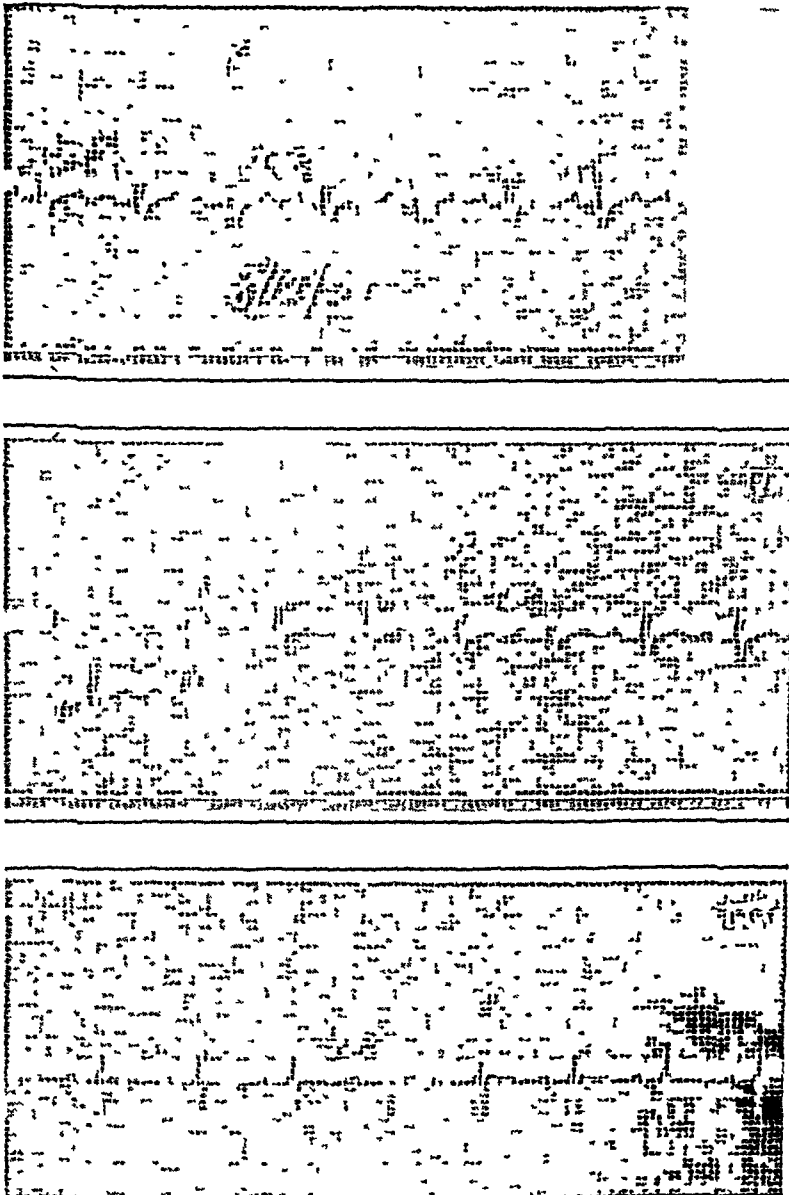


FIG 4 Electrocardiogram taken 7/12/29 showing very low T waves, PR interval 0.2, negative P<sub>2</sub>.

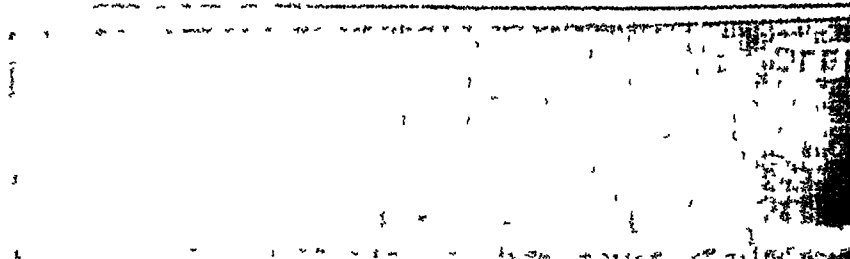
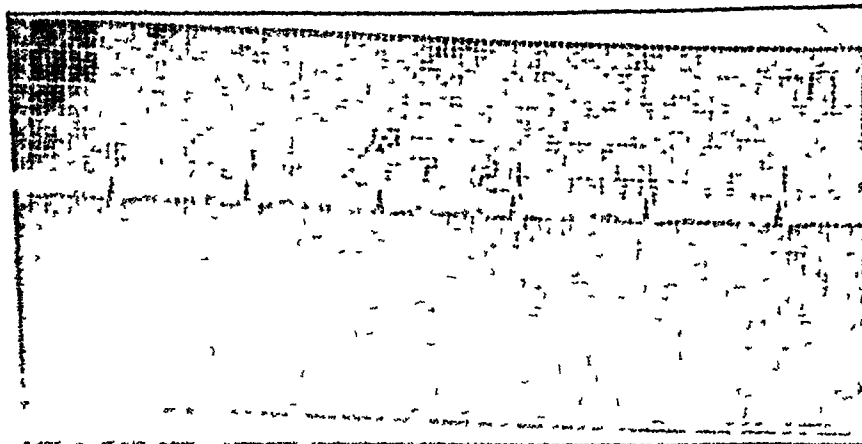
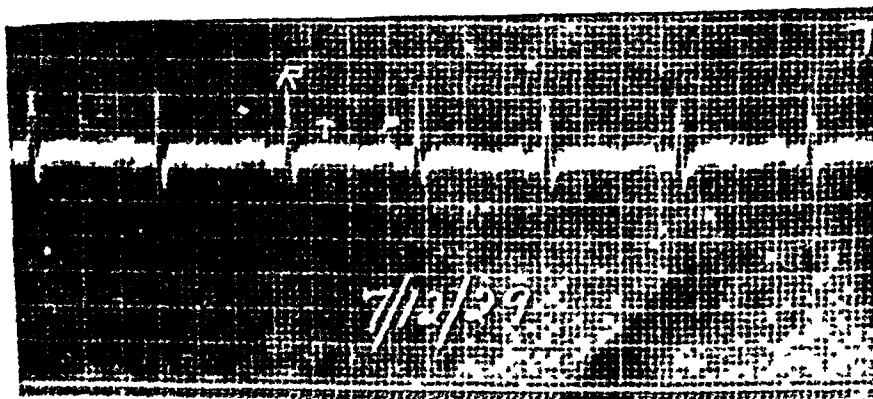


dema or myxedema heart may have angina attacks that disappear after thyroid medication and it is not impossible to conceive of the pain appearing after thyroid medication on physiological and pathological grounds as well as from purely coincidental causes

The first cases reported by Zondek had normal blood pressures All of our

cases have had normal blood pressures although one of them developed hypertension during treatment, which disappeared when the dosage of thyroid was reduced

A few cases have hypertension<sup>s</sup> at the beginning of treatment, and with the reduction in size of the heart to normal and clearing up of the myxe-



dema, the blood pressure drops to normal or nearly normal

Since the appearance of Fahí's paper in this country, several additional cases have been reported by others, but several internists of note claim it is a very rare condition, while a few have even denied its existence. This is difficult for us to understand. Out of 12 cases of myxedema seen in this clinic during the

past five years, nine have had myxedema heart and eight have responded to treatment by a reduction in size. In the one case where we have had a failure, we consider it partly the fault of the patient who would not remain a sufficient length of time in the hospital, and who would not take an adequate amount of thyroid.

Most certainly there are many cases

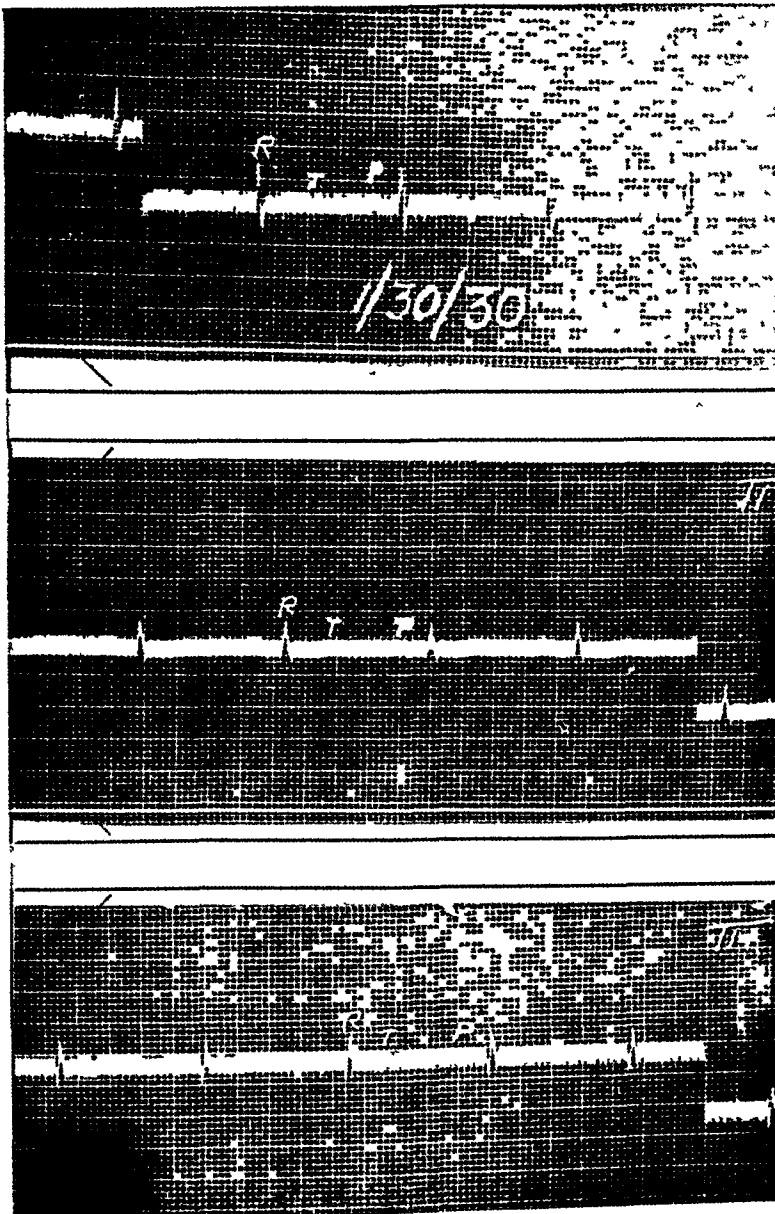


FIG 6 Electrocardiogram taken 1/30/30 showing iso-electric to very low T and P waves, PR interval of 0.2 to 0.22 and very low potential of QRS in all leads

of depressed basal rate which are not due to deficiency of the thyroid, only 45% of the basal rate can be accounted for by the thyroid gland. Other glands of internal secretion play a rôle. When we speak of myxedema, we do not speak of a patient with a depressed basal rate, but of those with symptoms and signs of myxedema as well as a depressed rate.

As to the pathology of myxedema heart, it can be said that no definite pathological picture is known.

A question that naturally arises is, how does thyroid act? The best evidence I know of is from work done in Frederick Mueller's<sup>9, 10</sup> laboratory where it has been shown that thyroxin and thyroid extract added to the perfusion fluid of an isolated frog heart causes an increase of the amplitude of the beat.

Some men<sup>11, 12, 13</sup> have sounded a warning on the danger of thyroid treatment in these cases because of putting a strain on a damaged heart by increasing the metabolism. A case has been

We are now using fresh preparations of Armour's thyroid extract, starting with 1 grain twice a day and gradually increasing to 1 grain five times a day. This dosage is decreased or increased according to the basal metabolic determinations and any untoward or disagreeable symptoms that may arise. In eight cases at this clinic, there have been no deleterious results from thyroid extract. In fact we have seen heart failures clear up, and the patient return to a normal existence. Some of them have been followed for five years, and none of them complained of heart symptoms except when they neglected to take thyroid or took too much. The patient must see a doctor once a month for a check of his pulse rate, basal metabolism, and for an evaluation of his subjective symptoms. In the hands of a doctor, who constantly watches his patient and is competent to evaluate cardio-vascular symptoms, we do not think there is any danger in the use of thyroid extract.

heart dilates and can again be brought to normal size by thyroid. This result cannot be secured with digitalis.

5 Enlarged hearts in myxedema, that do not decrease in size on thyroid, may be due to coronary disease, hypertension, or other causes.

6 Changes in electrocardiograms are discussed and explanations offered for these changes.

7 Theories to explain attacks of angina are given.

8 No definite pathological picture of myxedema heart is known.

9 The treatment of myxedema heart is discussed.

For references, the reader is advised to see the bibliography at the end of an excellent review of myxedema heart by Holzman, which is given below, together with a few additional references, some of which have appeared since Holzman's paper.

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# Foreign Bodies in the Stomach\*

By ANDREW B. RIVERS, M.D., *Division of Medicine, The Mayo Clinic,*  
and

HUGH L. DAVISON, M.D.,  
*Fellow in Surgery, The Mayo Foundation, Rochester, Minnesota*

THE discovery of foreign bodies in the stomach in the course of roentgenologic investigation or laparotomy is not uncommon. The literature on this subject is extensive and includes case histories describing the discoveries of a most amazing variety of substances retained in the human stomach. Wölfler and Lieblein reviewed 1184 cases of foreign bodies in the stomach and small bowel.

In this paper we shall report ten cases in which operations were performed for foreign body of the stomach, and three other cases contributed by Dr. O. Heyerdal of the State Hospital for the Insane at Rochester, Minnesota. We have not included in the paper the numerous instances in which patients examined at The Mayo

bezoars, phytobezoars and mineral bezoars, and (3) foreign bodies deposited in the stomach from the exterior, through surgical or violent wounds or from adjacent organs through fistulas, such as gallstones.

*Swallowed Objects*—Children frequently swallow small objects such as needles, pins and screws. Small, blunt objects which reach the stomach are frequently passed through the intestinal tract without much difficulty. Needles are more likely to cause abscess and perforation, especially if an emetic is given. Occasionally needles that have been swallowed will be found in parts considerably removed from the stomach or intestine, such as the region of the knee, or in the thorax.

Even blunt objects may cause ulcers or perforation

*Bezoars*—A bezoar is a calculus or concretion found in the stomach or intestines of some animals, formed of concentric layers of mineral, vegetable or animal matter deposited around some foreign substance which serves as a nucleus. In medical literature, almost any type of foreign body in the stomach is termed a bezoar. There is much evidence to suggest that the word has its origin either in the Persian word "pad-zahr" or perhaps in the Arabian word "bezah."

The Persian word "pad-zahr" is divisible into two words "pad" meaning "counter" and "zahr" poison, thus an antidote for poisons. Substances found in the entrails of animals, even to modern times, were considered as antidotes for various poisons. These bezoars were highly prized because, not only was it assumed that they had intrinsic value as curative agents, but mystical powers were ascribed to them so that they were worn as charms to ward off diseases. In the seventeenth century it was written<sup>4</sup> "The bezoartick is the present cure for all poisons and feavers. Extracts were also made and taken as medicines to cure various diseases. The most commonly found bezoars are the phytobezoars (plant-bezoars) which are built up mainly of vegetable matter, the indigestible substances of foods, such as seeds and fibers, are the structures around which most of these bodies are formed. The literature includes numerous cases in which patients have drunk paint or varnish in order to get the effect of its alcohol content. The included shellac in

some instances would act as a binding substance on the vegetable contents of the stomach, forming a foreign body which would fail to pass out of that organ. There are other instances in which the shellac alone formed a rather firm foreign body within the stomach, the tumor at times assuming large proportions.

Probably the most frequent source of gastric bezoars in the United States is the persimmon. The sticky juice and pulp of this fruit have a high content of pectin and gum, and it is probably because of this that bezoars occasionally develop following the ingestion of unripe persimmon.

Some solid concretions found in the gastro-intestinal tract are formed mainly by salts of calcium and magnesium. These are found more frequently in the small intestine than in the stomach. Occasionally they become large and may lead to serious complications such as obstruction or perforation.

A trichobezoar is a foreign body made up largely of hair. If this contains, as it usually does, vegetable matter, it is called a trichophytobezoar. The habit of some nervous or hysterical patients of swallowing hair occasionally results in the development of hair-balls in the stomach. These usually take the shape of the stomach. It is extremely unusual that hair-balls are found in the intestines, although a prolongation of the intragastric strands of hair may extend into the duodenum. The size of these accumulations of hair may be remarkable. The literature includes an instance in which a hair-ball weighed five pounds.<sup>5</sup> Frequently these accumulations cause marked dilatation of the stomach. The gastric wall may be thin,

and occasionally there is an associated gastric ulcer. The tumors are usually hard, due to the consistent packing together of the swallowed hair, and due also to the fact that detritus of all sorts becomes enmeshed in the hair-ball.

*Foreign Bodies Entering the Stomach Through Fistulas, or Puncture Wounds, and Those Left in the Gastro-Intestinal Tract Following Operation*—The development of fistula between the biliary duct system or the gall-bladder and the stomach may result in the appearance of a gallstone in the stomach. Such fistulas are much less common than those connecting the gallbladder or bile duct and the duodenum.

Occasionally these gallstones will cause intestinal obstruction. A drainage or feeding tube may drop into the stomach through an external fistula. This, however, usually passes through the intestinal canal without untoward result.

Occasionally a sponge, a probe or some instrument used during surgical

dren convulsions, following the swallowing of large objects. In others there is only a feeling of discomfort or a sensation of epigastric fullness. The appetite may become capricious or may be totally wanting. Diarrhea may become a troublesome symptom.

*Symptoms Arising Secondary to Presence of Large Foreign Bodies*—Foreign body may lead to weakness, loss of weight and strength, dehydration and anemia.

*Disturbances of Motility*—The flatulence, pain, nausea and regurgitation complained of by some patients are attributable to disturbances of the normal gastric motility. There may be marked delay in the emptying time of the stomach.

*Absorption of Poisonous Substances From Swallowed Objects*—Enough copper or lead may be absorbed from foreign bodies to give definite symptoms of metallic poisoning. This has been noticed especially in children who have swallowed copper or lead objects.

is frequently relieved by the ingestion of small amounts of food or soda

*Hemorrhage*—Sharp objects may produce hemorrhage because of the actual incision of the gastric or intestinal wall. Hemorrhage may also occur as one of the complications of the gastric ulcer which is so often found associated with the foreign body

*Penetration and Perforation*—Sharp objects may become stuck in the wall of the stomach or bowel, producing severe pains. Other objects, through repeated peristaltic efforts, may be pushed into the wall of the bowel, imbedding themselves therein, or even perforating through into the abdominal cavity. On the other hand, perforation may follow erosion of the gastric ulcer which is so often found associated with foreign bodies. Severe pain and increasing abdominal rigidity should suggest this complication. The symptoms of local or general peritonitis may develop

*Abscess Formation* — Occasionally erupted ulcers, or objects pushing into or through the wall of the viscus, will result in the formation of abscesses. The symptoms which suggest localized peritonitis then will develop and there will be the systemic reaction which abscesses anywhere will produce, such as pain, malaise, fever and leukocytosis

*Obstruction*—It is conceivable that many foreign bodies produce some delay in the emptying of the stomach or intestinal tract, producing constipation and a good deal of fullness and abdominal distension. It has been pointed out that occasionally diarrhea develops, this is probably due to enteritis or

gastritis. Constipation is more likely to be present than diarrhea. With increasing obstruction the symptoms become more definite, there being more distention and increasing difficulty in obtaining normal bowel movements. Complete obstruction at the pylorus due to a foreign body is not common, however, occasionally foreign bodies such as gallstones will cause a complete obstruction in the small bowel. The symptoms of acute obstruction are well marked and usually do not present great difficulties in diagnosis

#### DIAGNOSIS

A carefully taken history frequently helps greatly in making a diagnosis. In mentally defective patients, a history of swallowing one object should lead to the suspicion that other objects have been swallowed previously. The development, then, of gastro-intestinal symptoms of any nature should promptly lead to careful investigation with that in view

In children who are known to be swallowers of hair the possibility of a hair-ball must always be borne in mind in evaluating symptoms of a gastro-intestinal disturbance

The ingestion of large amounts of persimmons or of other fruits containing large amounts of gum and resin should lead to the suspicion of the possibility of phytobezoars

Occasionally the discovery of foreign bodies passed by rectum in cases in which the complaint is referable to the gastro-intestinal tract will lead to the correct diagnosis. No definite syndrome is characteristic of any of the foreign bodies of the stomach. The frequent association of gastric ulcer in



such cases makes the symptoms of this complication more likely to occur than in any other one syndrome.

Freely displaceable tumors in the epigastrium, which are not particularly tender, may lead to the diagnosis of foreign body. Sometimes two tumors of similar consistence, and apparently with similar general characteristics, are palpable. This again should suggest the probability of foreign bodies. Large, displaceable tumors in the epigastrium, such as those caused by hair-balls, occasionally because of their physical characteristics, aided of course by the history of hair swallowing, make possible the diagnosis of this condition preoperatively.

By far the most important aid in the diagnosis of such a condition is the roentgen ray. Usually even semi-opaque objects and even hair-balls can be discovered. The discovery of obstructed regions may also be a help in localizing foreign bodies which are causing definite symptoms.

Laparotomy is often advised in these cases because of an indeterminate type of mass or because of an indeterminate type of obstruction caused by one of the foreign bodies, and this is not infrequently the only way of being absolutely certain of the type of lesion which has caused the trouble.

The case has been reported, with stress on the roentgenologic aspects, by Camp.

*Case 2*—A man, aged twenty-four years, while hunting, ate about a quart of persimmons. A persimmon bezoar resulted. The case has been reported by Balfour and Good.

*Case 3*—A man, aged thirty-seven years, who was accustomed to eating large quantities of persimmons while playing golf in Mississippi complained of gastric distress. Two persimmon bezoars were removed from his stomach at one operation. The case has been reported by Droegemueller.

*Case 4*—A woman, aged thirty-two years, had been in state asylums for nervous and mental disease three times because of temporary insanity. There was no history of any previous illnesses of significance. The patient entered the clinic complaining that at intervals of several months she had had attacks of sudden, severe pain in the epigastrium. The attacks lasted about two weeks and were accompanied by nausea, vomiting and occasionally by fever. The pain was often referred over the entire abdomen, but the maximal distress was on the left side below the margin of the ribs. Apparently she had not lost weight and at the time of examination she appeared to be sane.

There was a freely movable mass in the left upper part of the abdomen. Roentgenologic investigation of the colon gave evidence of redundancy of the transverse colon and sigmoid, nothing else of significance was found. Because of the possibility that the mass found on examination might be kidney, cystoscopic examination was done and pyelograms were taken but results were negative. It was thought that the mass might be liver, spleen, and operation was ad-

domen, the size of 'a small orange,' which could be shifted from side to side Two to three weeks before registration she began having upper abdominal cramps lasting from a few minutes to half an hour She was constipated and this trouble was increasing Occasionally she had nausea and vomiting but no other gastric distress There was no bleeding from the bowel, and no hematemesis A roentgenogram of the stomach gave evidence of a large ulcer of the lesser curvature at the angle, probably malignant, there was marked obstruction A diagnosis of extensive carcinoma of the stomach and marked secondary anemia was made

Exploration revealed normal gastric walls except for changes characteristic of gastric ulcer, and a large tumor To mobilize the stomach was difficult because the gastric ulcer was attached to the liver The ulcer

was exposed through a large opening in the gastrocolic omentum From the extent of it, an inoperable tumor was suspected, probably a lymphosarcoma On continued palpation, the tumor was found to be rather doughy and because of the fact that very few nodes were involved, the stomach was opened and a hair-ball was removed The crater of the ulcer was about 4 cm in diameter, and it was considered that it might be malignant Because of the condition of the patient and the condition of the tissues, it was thought best to close the opening, give medical treatment and allow the patient to go home for a month or two

A letter dated January 10, 1928, from a friend of the patient stated that the patient was perfectly well, eating all kinds of food without gastric distress

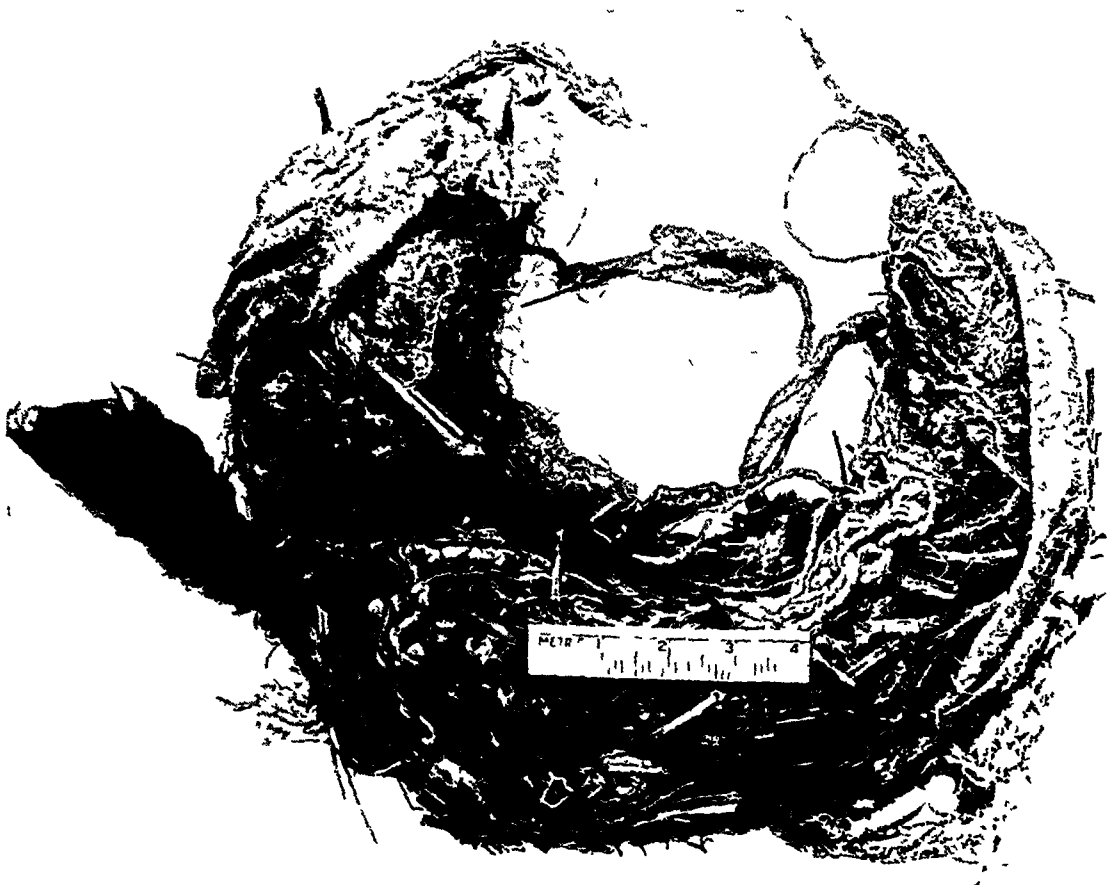


FIG 1 Gastric bezoar, consisting of hair, string and cloth It was 25 cm long and weighed 240 gm

*Case 6*—A girl came to the clinic complaining of constipation, and of an abdominal tumor that had been noted two weeks before. She had been well until about ten days before, when she had a "bilious attack," headache, constipation, drowsiness, and slight fever. That same evening she noticed some abdominal pain. The next evening she was nauseated after eating greens. Then generalized cramp-like pain through the abdomen developed. She went to bed for one day. She gave a history of being restless at night and of pulling and chewing hair.

General examination revealed a large, freely movable abdominal mass. The mass was irregular, crepitation was elicited, and it was easily displaced to any part of the abdomen. A cyst was suspected and operation was advised.

A large hair-ball that almost filled the stomach was removed.

*Case 7*—A man, aged fifty-one years, came to the clinic complaining of "heart

burn" and vomiting of all foods, of six months' duration. Six months before admission he had had a rather sudden burning sensation at xiphoid process, with radiation to the right of the sternum and up into the neck. He seemed to fill up to the xiphoid region and then would vomit. When this difficulty was first noticed he had as much trouble with liquids as with solid foods. He would be free from trouble for a few days and then attacks would come on again. The last attack had continued for three weeks. He had lost about 7 pounds in weight. He had had no trouble with his stomach since an operation for ulcer seven years previously. He did not know exactly what had been done at this operation.

Roentgenologic examination gave evidence of cardiospasm with slight dilatation of the esophagus. There was deformity of the duodenum, probably due to plastic operation. On bronchoscopic examination there was no obstruction to a number 41 French olive-tipped



bougie The thread broke when an attempt was made to pass a number 55 French sound Three days later a number 55 French sound was passed, with a moderate amount of pain Eight days later the patient seemed to be relieved of all trouble Roentgenologic examination of the esophagus then was negative He was advised to return if he had more trouble

The patient was readmitted five months later with approximately the same complaints as before He was completely relieved by dilatation of the cardia and was dismissed

Five months later, roentgenologic examination of the esophagus gave practically

negative results One year later the patient's chief complaint was cramps in the stomach of four months' to one year's duration He had been kept in bed for two months The pain came on at intervals and was usually more severe from half to one hour after eating, and at night He stated that for three months he had vomited practically everything he ate The food seemed to stick in the midthoracic region and in the region of the cardia, and then to slide through into the stomach He seldom vomited water He had lost 10 pounds in weight in four months He took a cathartic every two days He had to urinate three or four times each night for two months

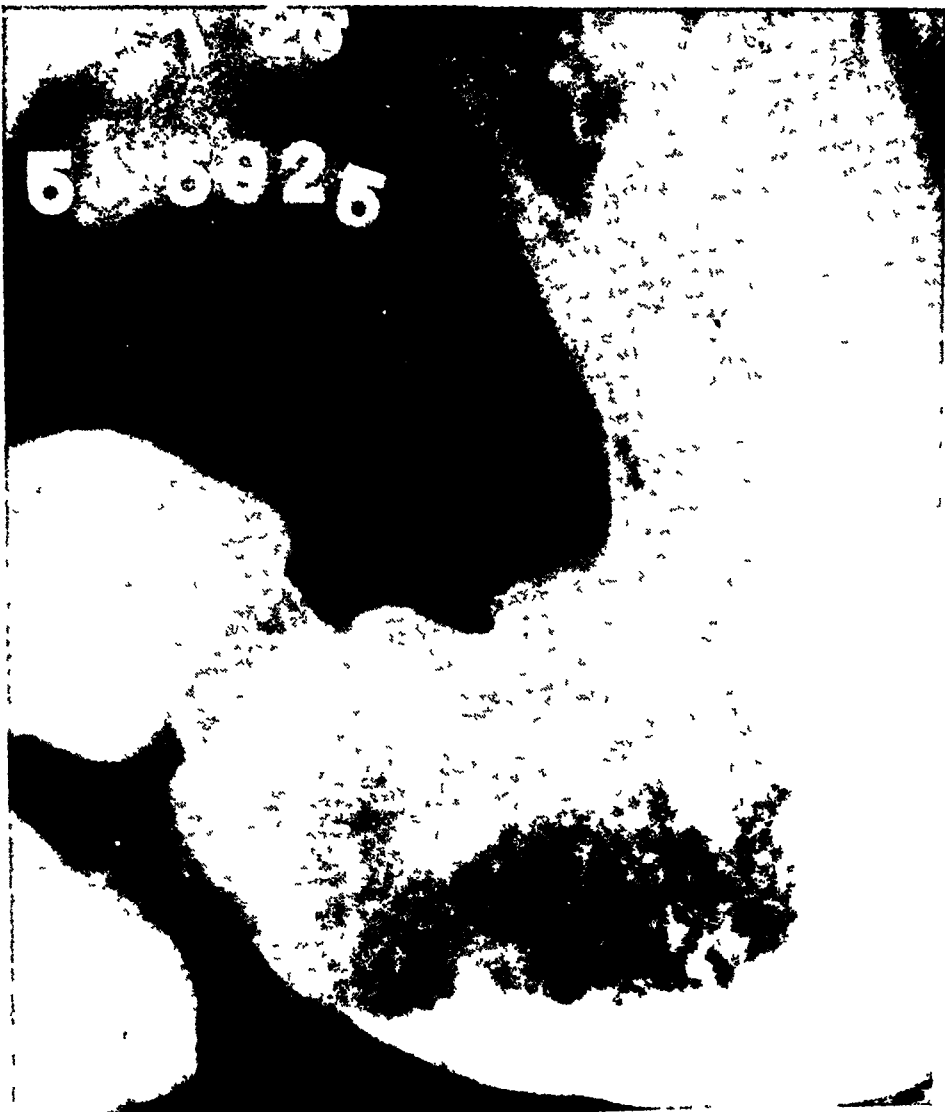


FIG 3 Gastric ulcer associated with the hair-ball shown in Fig 2

On examination of the abdomen, definite peristaltic and anti-peristaltic movements could be seen synchronous with the patient's cramps. An irregular mass was palpable. Roentgenologic examination of the esophagus and stomach gave evidence of obstruction at the cardia, apparently malignant. There was duodenal obstruction 15 cm from the pylorus, the opening made at gastroenterostomy was not free. Esophagoscopy examination gave negative results.

Exploration of the stomach and duodenum was performed eight days after admission. An operative diagnosis was made of foreign body (fish line) in the stomach, pyloric obstruction, jejunal ulcer, subacute duodenal ulcer, and partial obstruction of the gastroenterostomy opening. The patient had a large stomach and duodenum with a subacute, contracting type of lesion almost immediately below the pylorus. In the stomach itself was a mass about 5 by 6.5 cm lying near the small posterior gastroenterostomy opening. This felt like a foreign body and was rather suspected of being twine before it was opened because of the fact that the twine had broken during one of the dilatations of the cardia more than a year previously. The strands of twine extended down into a large proximal loop. On the inner side of this loop about 8 or 10 cm from the gastroenterostomy opening was a perforating lesion with rather extensive inflammatory product about it, but

removed from the pylorus was "inflammatory hypertrophy."

Three weeks later the wound was completely healed and the patient felt well. He could eat well and had no indigestion or dysphagia.

*Case 8*—A young married woman came to the clinic because of an attack of nausea, vomiting and pain, with exacerbations of severe pain in the lower right quadrant of the abdomen. Soreness and pain occasionally radiated through to the back. Two years later the patient returned to the clinic complaining of spells of vomiting, regurgitation before and after meals of a greenish-yellow, bitter fluid and on several occasions of particles of undigested food. Dizziness always preceded vomiting; menstruation made the vomiting worse.

Function of the bowels was normal and the appetite was good. Before vomiting, the patient would have a sharp knife-like pain in the left side. She thought she noticed some jaundice after vomiting. The pain was rather indefinitely situated.

On exploration a perforated duodenal ulcer about 4 cm in diameter was found. It was buried in adhesions, was situated about 6 cm below the pylorus, and one point of a wooden toothpick was in the ulcer and the other projected into the stomach. The upper part of the abdomen was filled with adhesions. Chronic appendicitis was present.

separated, leaving the tip and a number 28 or 30 French long spindle between the two strictures

A Witzel gastrostomy was done and the olive and about 75 cm of the whalebone staff were removed through the opening on the anterior surface of the stomach. The opening was sutured with two layers of chromic catgut. The new opening was left just large enough for a catheter to be inserted.

*Case 10*—A woman, aged twenty-three years, was an inmate of the Rochester State Hospital because of dementia praecox.

September 22, 1915, the patient was operated on at The Mayo Clinic. Seven teaspoons a hair pin, a straw and some hair were removed from the stomach. The case has been reported by Balfour.

For the following three reports of cases we are indebted to Dr O Heyerdale of the Rochester State Hospital.

*Case 12*—A man, aged fifty years, affected with a manic depressive type of psychosis, swallowed hair pins, bolts and nuts. Finally the patient began to complain of abdominal pain, distress and constipation, and he became rundown physically.

The patient was put to bed on a diet chiefly of oatmeal and soft foods, and passed a large number of these objects. After passing numerous bolts and so forth, he felt relieved and was dismissed from the infirmary. The patient occasionally swallowed more foreign bodies, mainly bolts, and after a few months he was again hospitalized and the previous treatment was again instituted. This procedure has been repeated three or four times.

*Case 13*—A man, aged thirty-four years, was a victim of a manic depressive type of psychosis.

The patient scraped out with a knife the edible portion of a squash until only the

hard rind remained. This he rolled up tightly into a cigar-like mass. He managed to push this mass into his stomach. For some time he had no untoward symptoms. Weeks later, epigastric pains developed. At one time he vomited blood. Soon after these symptoms began he died rather suddenly.

Necropsy disclosed that the rind had sawed a hole through the gastric wall, producing hemorrhage and fatal peritonitis.

*Case 14*—A man, aged forty-five years, who had a manic depressive type of psychosis, broke a wire from the bed spring and swallowed it. The wire was in the shape of the letter T. He was given a diet of oatmeal and soft food and within a few days he passed the swallowed body by rectum. He apparently suffered no untoward effects from the experience.

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# Chronic Sinus Infection in Relation to Systemic Disease\*†

By NOBLE W. JONIS AND FRANK B. KISTNER, *Portland, Oregon*

WHEN one refers to chronic hyperplastic sinusitis, and especially to the non-purulent form of chronic hyperplastic sinusitis, as a focal infection of importance, one treads upon debatable ground. Many rhinologists of note believe that chronic inflammation of the nasal accessory sinuses plays little, if any, role in the causation of systemic disease<sup>1</sup>. Although our work during the past five years has led us to other conclu-

sions, yet we have respected these views, and they have, we believe, tempered our enthusiasm and have influenced the forming of our opinions.

The work now presented has been gleaned from an unfinished analysis of about 750 patients upon whom radical sinus operations have been performed for varying diseased states. The patients group themselves into more or less well defined entities, such as anemia, arthritis, bronchitis and asthma, cardio-sclerosis, general malaise, and a neurological group consisting of chorea, spasmodic tic, periodic hyperpnea, etc. We shall illustrate these different groups of diseases by short

\*Abstract of clinic held February 14, 1931 at the Fourteenth Annual Clinical Section of the American College of Physicians, Minneapolis, Minnesota.

†From the Departments of Medicine and

*Case 1* BB, age 13, April, 1928 Chronic bronchitis began in this patient with acute colds before two years of age. The child has never been free of it. Seven times she has had pneumonia three times the pneumonia was diagnosed lobar, the child having bloody sputum and the pneumonia lasting about nine days, and ending with crisis. She expectorates half an ounce of purulent sputum each day. Examination showed bilateral coarse râles and rhonchi with thickening of the peribronchial shadows in the lower lobes of the lungs. There was no evidence of tuberculosis. Tonsils and adenoids had been previously removed. There was present a generalized pan-sinusitis. On April 7, 1928, a double radical antrum operation was performed. Free pus was found in both antra. The linings were uniformly thick, red and edematous (Fig 7). The posterior ethmoid cells were opened from the antra on both sides. On May 7, 1928, there was a right frontal, ethmoid and sphenoid operation, and a left intra-nasal ethmoid operation performed. Free pus was found in all of the sinuses, together with polyp formation.

Cultures from swabs and tissues from the right antrum gave colonies of staphylococcus aureus, alpha hemolytic short chain strepto-

cocci, and long chain beta hemolytic streptococci. Swabs and tissue cultures from the left antrum gave staphylococcus albus, alpha hemolytic and beta hemolytic streptococci.

Through the summer the cough and expectoration disappeared. The patient had had much operative work done upon her head. At 9 years of age she had had a mastoid operation which healed successfully. At the age of 3 years her tonsils and adenoids had been removed cleanly. In November, 1926, both antrums had been opened and washed for a month, and in July, 1927, polypus had been removed from the right antrum intranasally. These temporizing operations upon the sinuses had had no effect whatsoever upon the progress of the chronic bronchitis.

*Case 2* RLG, age 54, April, 1923. The patient, who at the present time has a severe asthma, has been of special interest to us, for during years of observation we have seen a chronic asthma develop in one in whom there has been no evidence of allergy. It began, and recurred intermittently, with acute cold infections. At first merely a mild rhinitis appeared. Later polypoid swelling in the posterior ethmoid and sphenoid regions, which disappeared as soon as the acute colds were over, occurred. As re-infection took

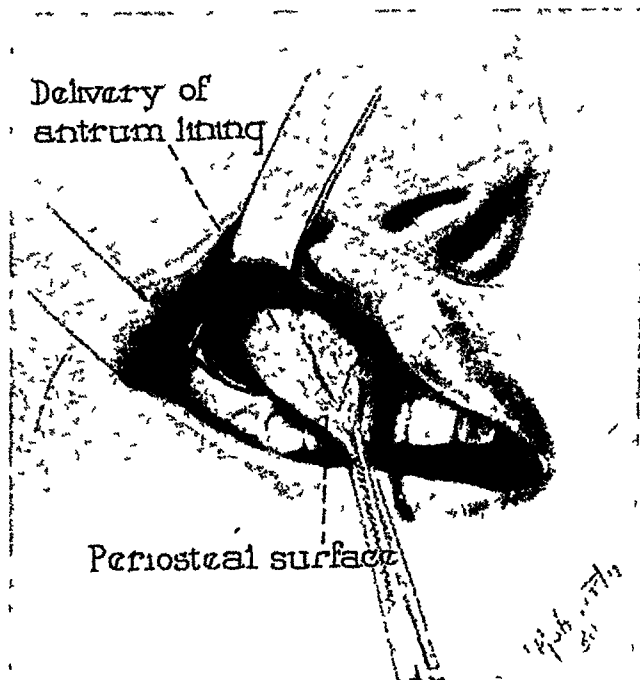


FIG 1 Shows the method of exenterating the antral membrane



place the growth of polyps throughout these regions and in both antra progressed to the point where massive polyp formation existed in both antra, and at the same time the asthma became protracted. There has been no radical operative work done upon this patient. Temporizing efforts have been made to give him relief by the periodic removal of some of the larger polyps and by the use of a vaccine prepared from cultures. The importance of this case to us has been watching the evolution of a severe bronchial asthma, not associated with allergy, but associated with the development and progression of a chronic hyperplastic sinusitis.

Case 3 Mrs TMB, age 62, May, 1927. This patient has suffered severely from asthma for 6 years. Exacerbations are re-

lated to head colds and are not related to seasonal changes. Hay fever has also been present for 10 years. Attacks begin in July and continue through August, the patient being free from these symptoms for the balance of the year. She is sensitive to reed canary grass, squirrel tail, red top, alder and aspen. Relief from the hay fever has been obtained by going to the sea shore. A general asthenia with much loss of weight has accompanied the asthma. The right antrum contained a purulent hyperplastic membrane with polyp formation. The left antrum had a smooth, generalized thickening of the membrane, and was half full of viscid mucoid material. The ethmoids and sphenoids were also involved. On June 10, 1927, a double radical antrum operation was per-

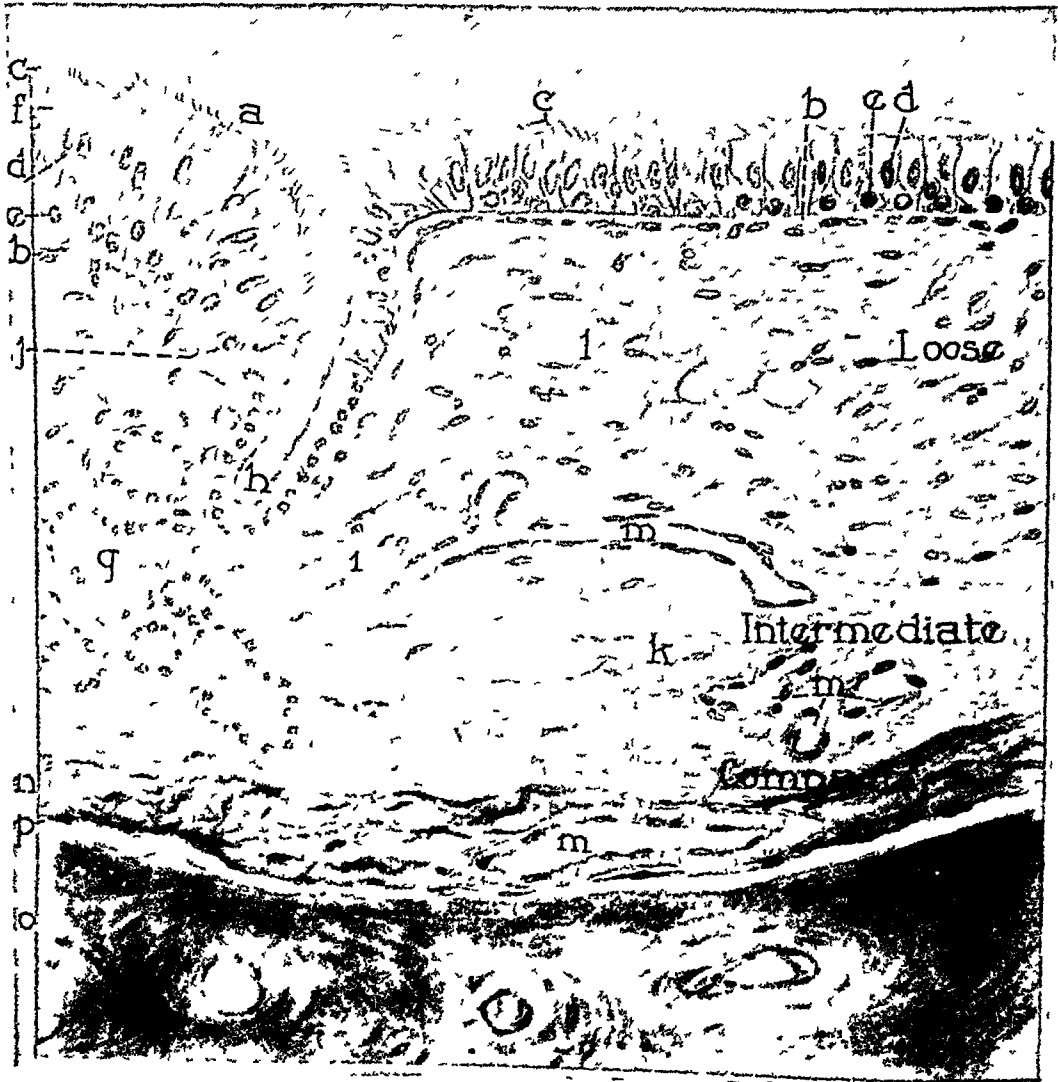


FIG 2 Diagrammatic drawing of the normal sinus membrane

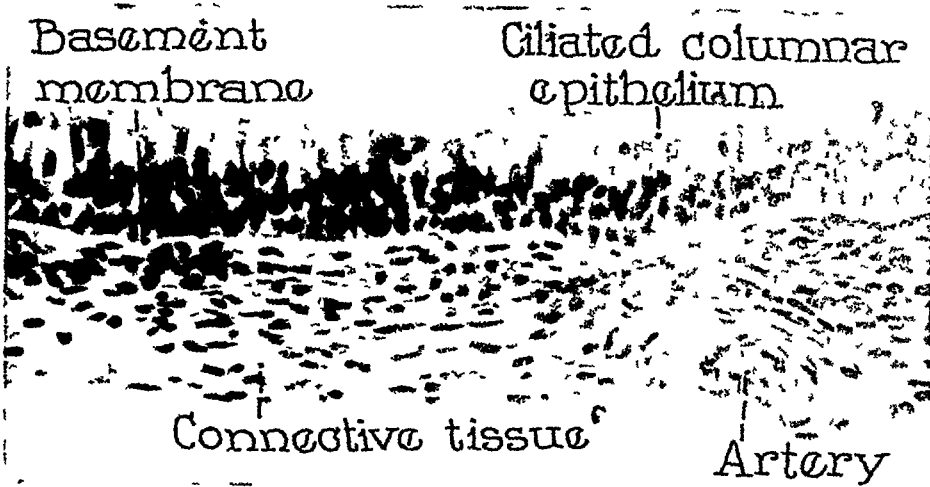


FIG 3

FIGS 3 and 4 Microphotographs of normal and diseased sections of ethmoid membrane taken from locations as shown in Fig 5—which is drawn to scale

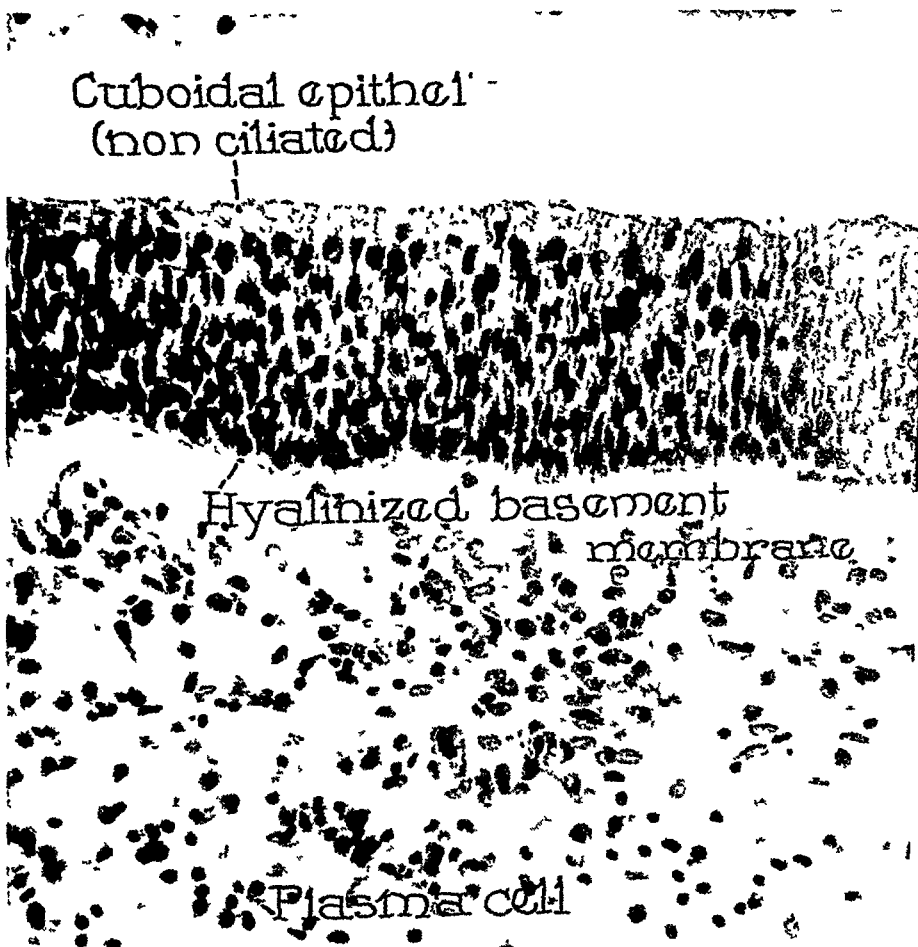


FIG 4

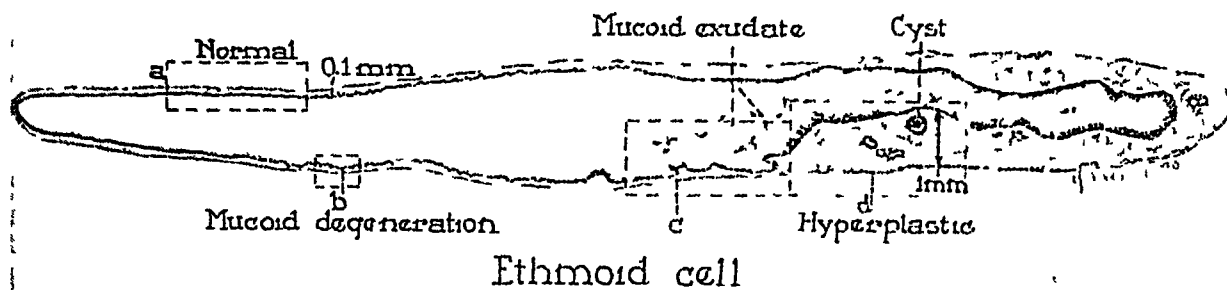


FIG 5

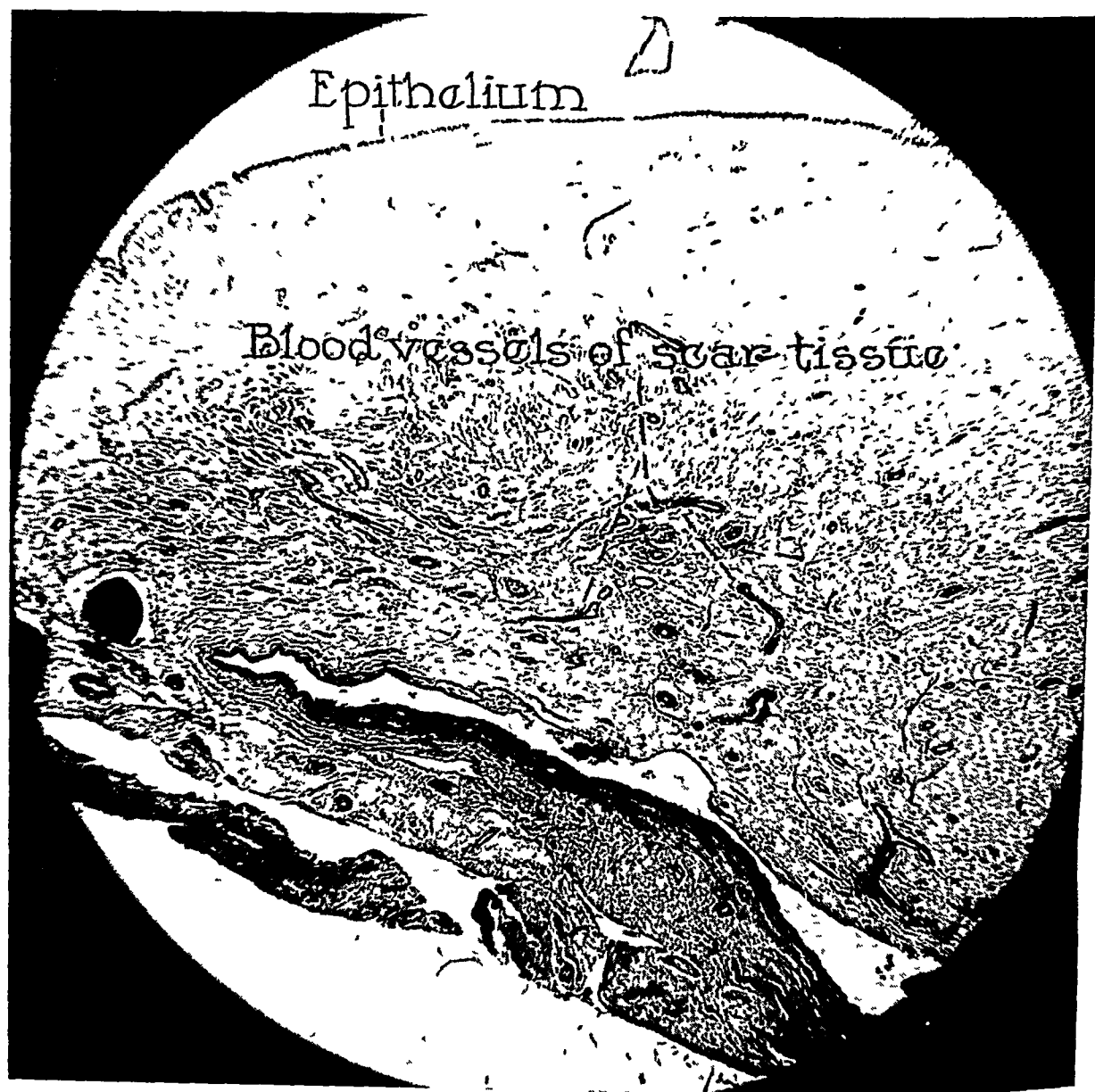


FIG 6 Microphotograph of section of healed antrum tissue—showing single layer of non-ciliated columnar epithelium and thick layer of scar tissue with fibroblasts and many newly and irregularly formed blood vessels. This portion of the diseased tissue had been removed intranasally two years before the present trans-antral operation.

formed, and on June 28, 1927, an intra-nasal ethmoid and sphenoid operation. Hyperplastic tissue, filling most of the ethmoid cells and both right and left sphenoids with free pus, was removed.

The patient was free from asthma until the spring of 1929, when it slowly returned, beginning with hay fever in May, associated with fever and a return of her head colds. October 27, 1929, a trans-frontal ethmo-sphenoidectomy was performed. There was pronounced polypoid thickening throughout the frontals and the anterior ethmoid cells which had not been reached through the intra-nasal route. The previously operated upon sinuses showed complete and satisfactory healing. Relief was again obtained from the asthma, but the patient is now being immunized with a vaccine obtained from the tissue removed at the last operation. *Pathological Report*. The right antrum—the wall is 2-3 mm thick and regular. The epithelium

is intact and of the pseudo-stratified columnar type and only moderately hyperplastic. The submucosa is greatly edematous and is densely infiltrated with wandering cells in which eosinophiles predominate. The remainder are mostly plasma cells and lymphoid cells. The infiltration decreases as the periosteum is approached. The left antrum—the wall is 2 mm thick. Microscopically it is similar to that of the right with certain exceptions. The epithelium of the mucosa has undergone mucoid degeneration and it takes a deep blue stain with hematoxylin. The same eosinophilic infiltration is present and there are also dense infiltrations of lymphoid cells.

Cultures from the tissues showed numerous beta hemolytic streptococci and a gram positive diplococcus. A rabbit inoculated with these mixed cultures and autopsied in 72 hours showed in the heart's blood and several joints beta hemolytic streptococci.

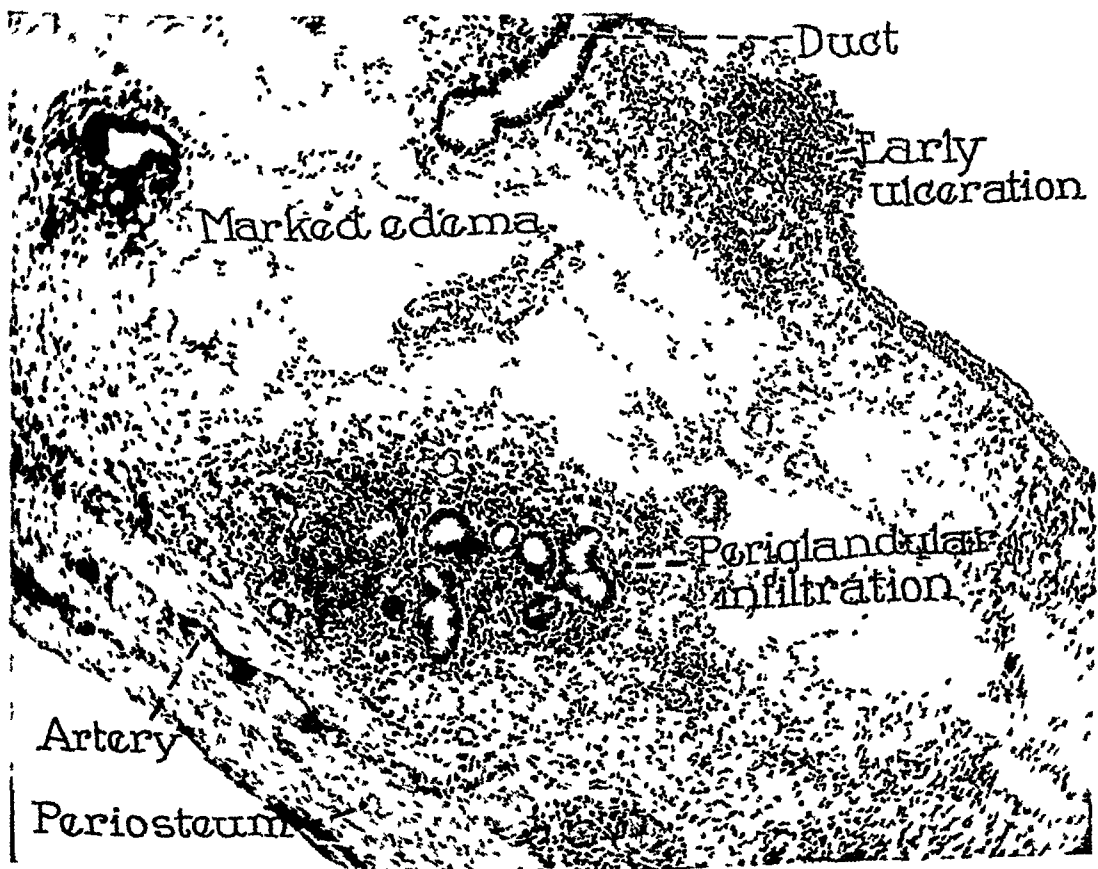


FIG 7 Microphotograph of section of antrum membrane removed from patient—Case No 1—bronchitis group

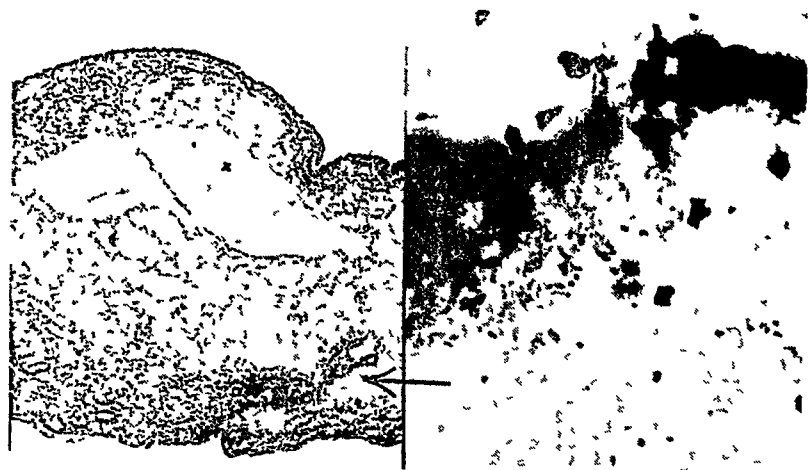


FIG 8 Microphotographs of sections of antrum membrane removed from patient—Case No 3—arthritis group Left shows hyperplasia of mucosa, edema and infiltration of submucosal layers Arrow points to site of diplococci shown on right

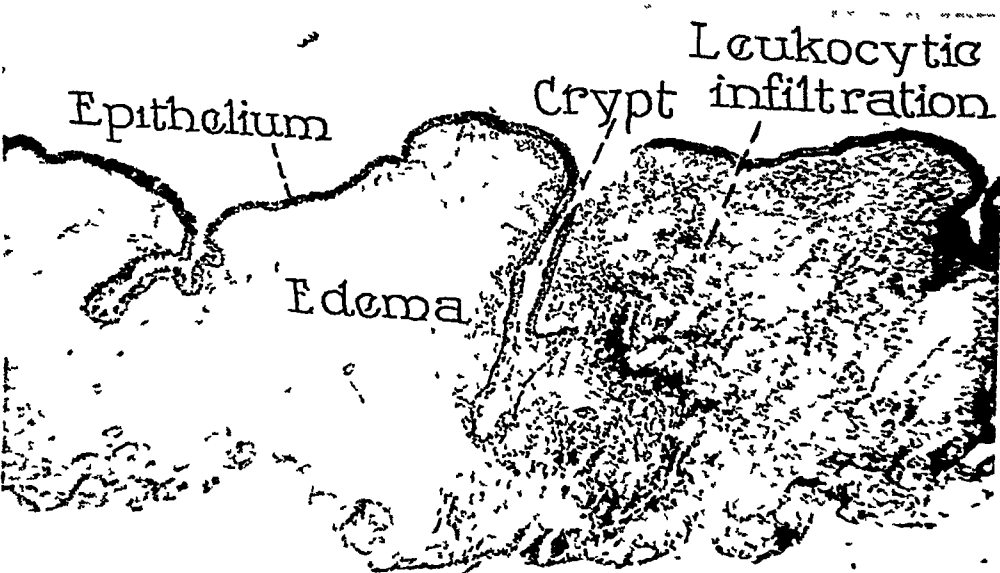


FIG 9 Microphotograph of section from a different portion of antrum membrane from same patient as in Fig 8

and a few gram positive diplococci. A stool culture November 4, 1929, in blood agar media showed many colonies of non-hemolytic diplococci and a few colonies of hemolytic streptococci.

*Case 4* Mrs GT, age 35 August, 1929. The patient has suffered severe attacks of asthma since an attack of influenza 8 months ago. Exacerbations have followed acute cold taking without regard to season. Examination showed a non-purulent, hyperplastic, generalized sinus disease. August 30th a double radical antrum and a trans-antral *ethmo-sphenoidectomy* of both sides was performed, with immediate relief. There was marked thickening of the lining membranes throughout, with large polyps within each antrum. There was no free pus. Cultures from the right and left antrums and sphenoids showed a moderate growth of

green-producing streptococci with a few colonies of staphylococcus albus. A rabbit inoculated with the 24-hour broth cultures was autopsied 48 hours later and showed no distinctive pathological lesions.

Late in December, 1929, following an acute head cold there was a slight return of the asthma. Some pus flakes were washed from the left antrum and a few granulations within the right sphenoid area were cauterized. Stool cultures were made which gave many colonies of a non-hemolytic diplococcus and numerous colonies of a green-producing streptococcus. Complement fixation with the non-hemolytic diplococcus was +4, with the green-producing streptococcus was +1. A sensitized vaccine filtrate was prepared from the two organisms. The subcutaneous injection of 0.02 cc of this vaccine produced a reaction characterized by a

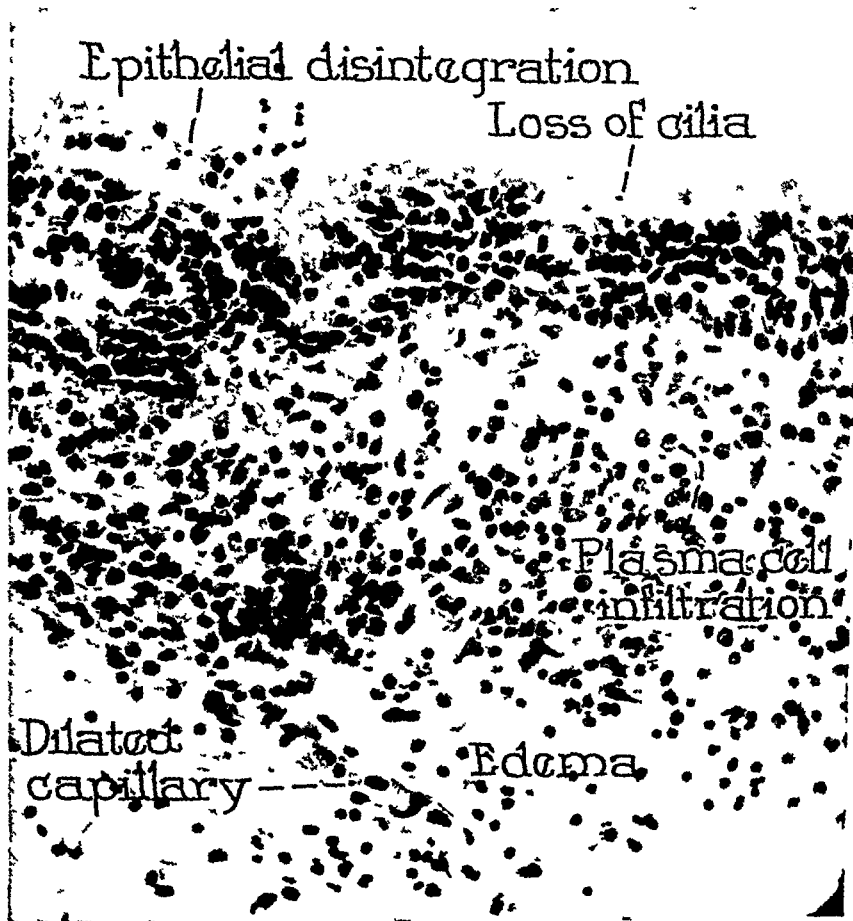


FIG 10 Microphotograph of section from antrum membrane removed from a patient suffering from acute chorea. The patient recovered rapidly following the operation.

sense of tightening in the throat, accompanied by wheezing. A dose of 0.01 cc did not produce such an effect, and the patient is continuing to use this dosage, administered once a week. Her asthma has again entirely ceased.

*Group 2 Chronic Septic Arthritis*  
A number of arthritis patients have sinus infections as causative or associated factors. Some of them have received such prompt relief of joint symptoms following removal of these infected tissues that no reasonable doubt existed as to the etiologic rela-

tionship. In others the sinus infection seemed to be but one of several focal infections.

*Case 1* IRC, age 44, November, 1927  
The patient has suffered chronic back pain referred into right and left sciatic regions for one year, confining him to bed most of the time. Examination showed a spinal arthritis with considerable lipping in the lower thoracic spine, partial bridging between the 10th and 11th vertebrae, and some proliferative changes about the 3rd, 4th and 5th lumbar vertebrae. Chronic non-purulent hyperplastic double antrum disease was found, and a double radical antrum opera-

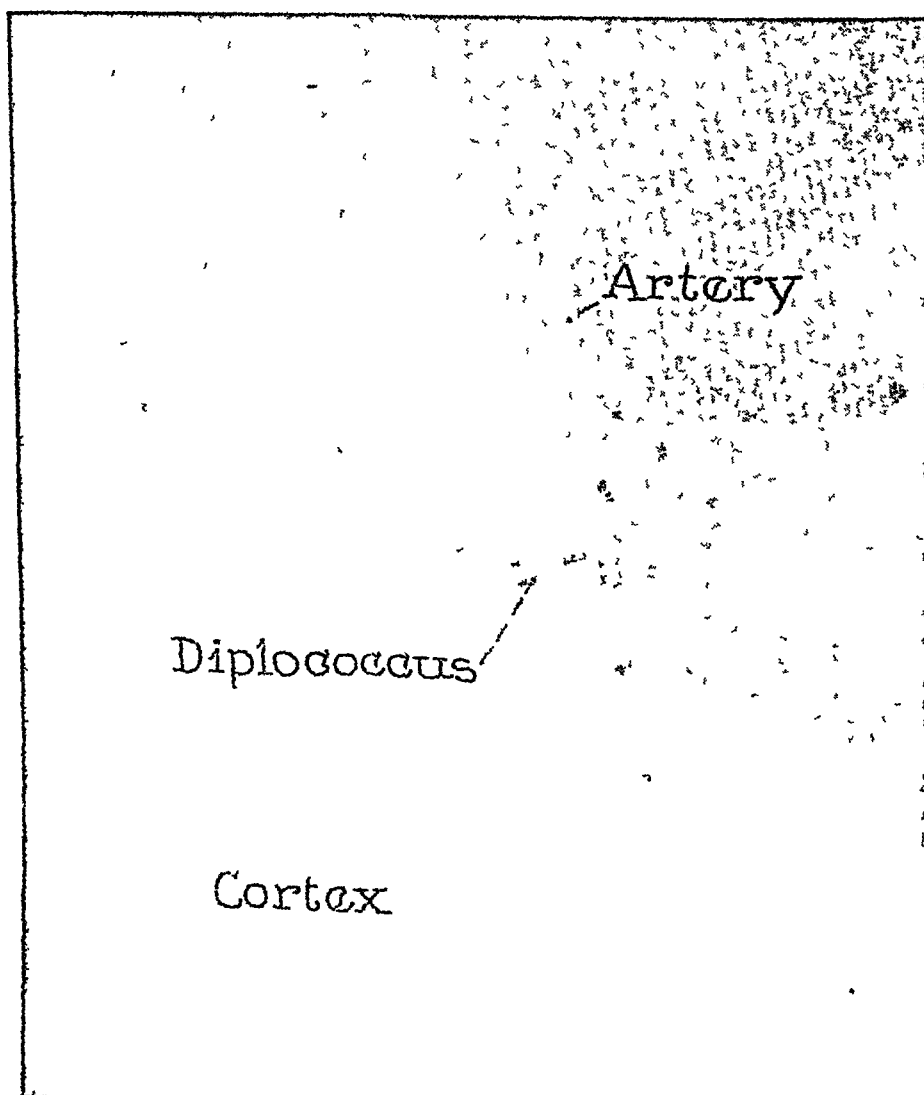


FIG. 11. Microphotograph of section of cortex of rabbit's brain inoculated intracerebrally with 0.2 cc mixed dextrose-brain broth culture of antrum membrane removed from patient No. 1—neurologic group. Many diplococci are seen in this section.

tion done December 3, 1927 A general thickening throughout both antrums existed, the membranes were edematous, fibrous and more tightly fixed to the bone than normal. Cultures from swabs and from the tissues from the right antrum showed a growth of hemolytic and green-producing streptococci. The left antrum swabs gave a growth of long chain, green-producing non-hemolytic streptococci and the tissues gave a growth of a few hemolytic colonies of streptococci

and a moderate number of green-producing streptococci. A rabbit inoculated with a combined mixture of the cultures showed arthritic lesions in both hind limbs, but cultures from these joints remained negative (The joint fluid alone was cultured)

Rapid improvement of the patient occurred following the operation, and he now reports himself practically free from pain and that he is able to carry on his farm work without difficulty



FIG 12

FIGS 12 to 17 inclusive Microphotographs of sections of antrum membranes removed from patient No 2—chronic atherosclerosis group. Note extensive fibrosis and thrombosis of blood vessels. Diplococci are shown on the surface of the mucous membrane, in the submucosa, within the wall of an arteriole, and in the coagulum of an arteriole's lumen.

NOTE The tissues are stained according to Lillie's modification of the Gram Stain (Lillie, R. D., The Gram Stain, Arch of Pathol 5 828-834, 28). Precaution is taken to prevent artifacts. The tissues are fixed immediately in formalin as they are removed in the surgery. After paraffin impregnation sections are cut 5 micra in thickness. These are mounted on clean slides using sterile water. The sections adhere to the glass by the intervention of any cementing substance, being brought into contact with the glass by the evaporation of the layer of water on which they are floated. The materials are covered to prevent air borne particles from falling on the sections, and the stains are freshly filtered



*Case 2* APW, age 39, January, 1929  
The patient has been entirely crippled, unable to work, and, for the most part, confined to bed for the past six months, during which time he has lost 25 pounds in weight and much strength. Most of the joints of the body have been involved, particularly both elbows, left knee and foot, and right knee, both elbows having developed contractures. Infected teeth had been previously removed. Cultures from the prostate were negative. A chronic purulent and hyperplastic double antrum disease was present, and was radically removed January 12, 1929, the lining being definitely thickened, edematous, and each antrum containing free

pus. Cultures from the tissue of the left antrum gave a mild growth of green-producing streptococci and staphylococcus albus. Cultures of the right antrum tissue gave greenish streptococci, a few staphylococcus albus and a few micrococcus catarrhalis. The rabbit inoculated with mixed cultures, autopsied in 48 hours, showed no lesions.

The stools cultured gave non-hemolytic green-producing streptococci and a few colonies of non-hemolytic pleomorphic diplococci. The patient's blood serum showed a complement titer of 2. The complement fixation with the above strains were, first, with green streptococci, +3, second, with diplococci, +2. A sensitized vaccine filtrate

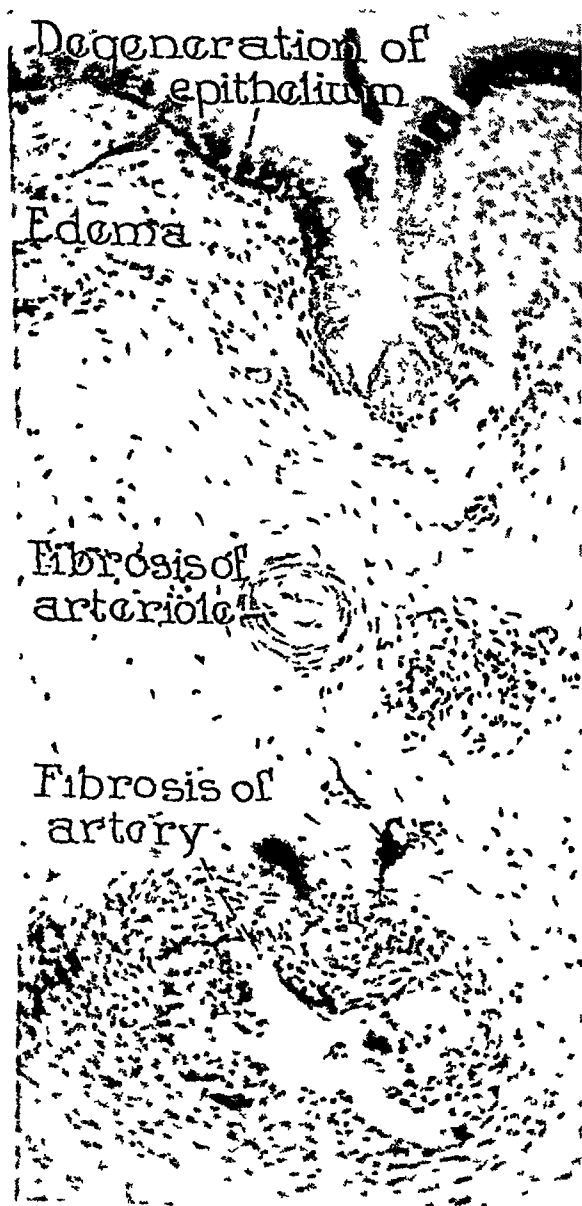


FIG 13



FIG 14

was prepared from these organisms. Seemingly this vaccine gave what we have looked upon as specific reactions and the use of the vaccine filtrate was continued at doses of 0.002 of a cc., a point beneath that dosage which gave a negative phase reaction.

The left elbow and the right knee still remain somewhat swollen and somewhat tender, but the patient reports continued improvement. About a seventy-five per cent recovery has been made by this patient following the operation and the use of the vaccine.

*Case 3* HS, age 49, March, 1928. For one year patient has suffered severely from chronic arthritis, affecting chiefly the back, ankles, right shoulder and hands, but with more or less pain over the entire body. All previously found foci of infection had been

removed. Examination of the sinuses gave only suggestive findings. The roentgen films both with and without lipiodol showed a thin lining membrane with the possibility of a cyst-like defect in the right antrum. An exploratory examination of the sinuses alone was advised, to which the patient consented. The right antrum revealed a cystic abscess extending along the lateral wall. A moderate generalized thickening of the membranes of the right antrum was found. The left antrum contained some free mucopus and the lining membrane was generally thickened and edematous throughout. Cultures from both antra gave a growth of a short chain diplo-streptococcus which produced slight hemolysis and slight green coloration of the blood agar. The cultures injected intravenously into a rabbit caused death in 24 hours. There was resulting

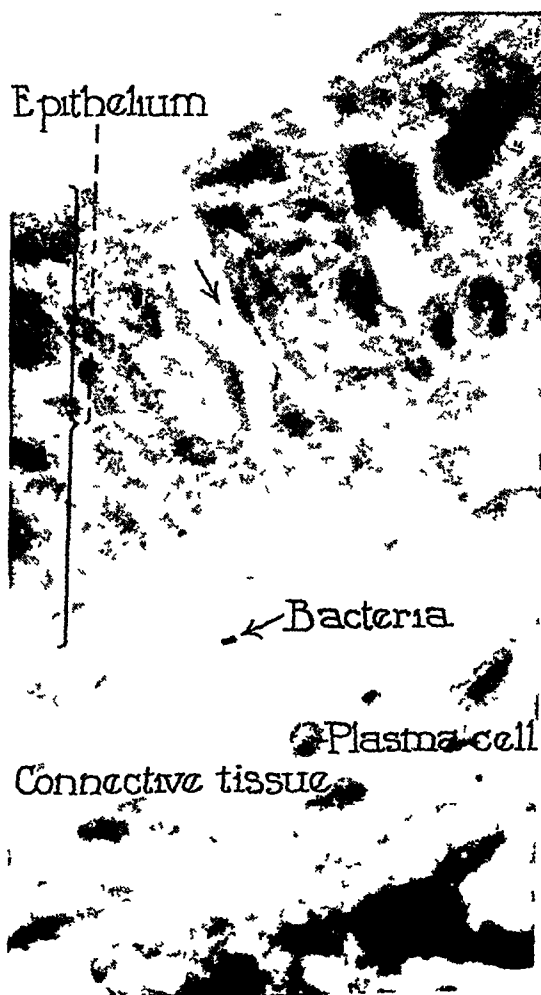


FIG 15



FIG 16

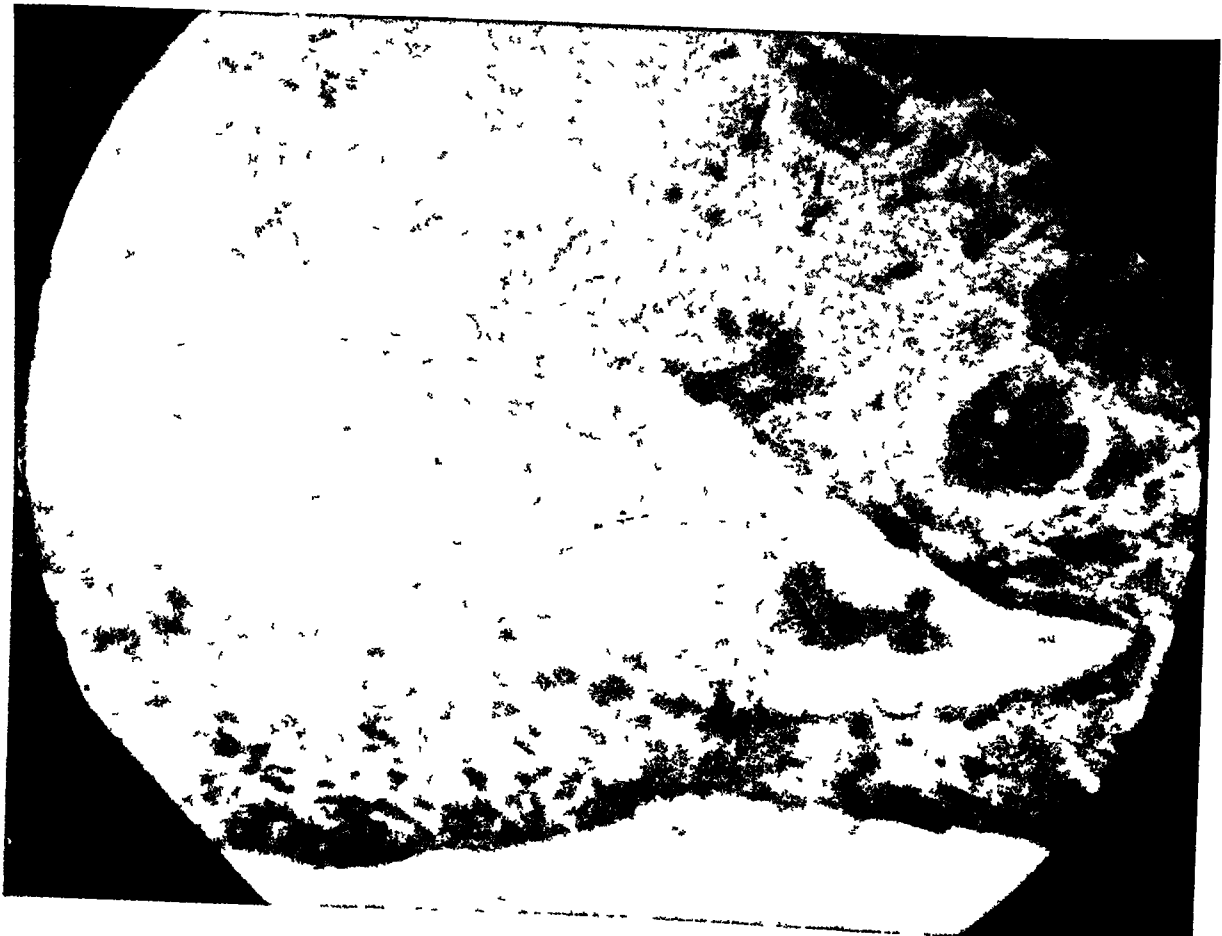


FIG 17

involvement of many joints, and a slight enlargement of both kidneys. Cultures from the joints gave a growth in pure culture of slightly green producing streptococci.

Recovery from the arthritis was unusually prompt in this patient following the operation, and for two years he has been well.

*Group 3 Chronic Anemia* Many patients suffering from chronic sinus disease have a moderate grade of secondary anemia which remains fixed until the infection is removed. Occasionally the anemia dominates the picture. The hemoglobin remains about 50 per cent and the red cells about 3 million in spite of all empiric methods of treatment. In a few cases of pernicious anemia the removal of an associated sinus disease has seemingly influenced symptomatic recovery.

*Case 1* Mrs FLW, age 48, October, 1927. The patient gives a history of gastrointestinal trouble for a year—pain, bloating, periodic constipation. She has had a pale color, and has been generally weak for a longer time. Examination revealed a chronic cholecystitis with complete non-filling of the gallbladder, and a secondary anemia of 50 per cent hemoglobin, 3 million red cells, and a seemingly normal differential count. No distinctive type of secondary anemia picture could be determined. There was present a chronic non-purulent hyperplastic double antrum disease.

It was found possible to relieve the gastrointestinal distress, due to the related motor disturbances, by means of a smooth diet, but the blood picture did not improve in response to therapy. Believing that the antrum disease was of more importance than the affected gallbladder, a double radical antrum operation was performed November 15, 1927, which showed the antra filled with polypoid hyperplastic tissue and thick mucus but no free pus. Cultures of the right antrum gave a growth of non-hemolytic green-producing short chain streptococci with a few colonies of hemolytic long chain streptococci. Cultures of the left antrum gave a growth of

non-hemolytic green-producing short chain streptococci.

Convalescence was prompt, and with the patient's convalescence a noticeable response in her blood picture was noted. She left Portland with a blood count of 89 per cent hemoglobin, 4.65 million red cells, and a color index of .95. Her blood picture has subsequently become normal and aside from occasional distress she remains well.

*Case 2* Miss TR, age 48, December, 1928. The patient has suffered off and on for three years with sore tongue, loss of strength, marked paleness, irregular bowel, and attacks of pain under the right costal margin. The blood picture and general physical examination were very suggestive of pernicious anemia. But added to this picture was marked dental sepsis, a chronic cholecystitis, and chronic hyperplastic antrum disease. Relief of the gastrointestinal symptoms was obtained by diet regulation. The anemia was slow to respond to therapy, and because the sinusitis seemed to be definitely of importance, a double radical antrum operation was done January 8, 1929. There was generalized thickening of the lining membranes with edema. Swabs and cultures from the antra gave a few colonies of staphylococcus albus and a culture of green-producing streptococci.

The patient's general health improved rapidly after the removal of this pus infection. It had not responded to a previous removal of her dental infection. She has become stronger, her blood picture is within reasonably normal limits, though still showing characteristics of a pernicious type. She continues to eat glandular meats daily. We think this patient's general health and blood picture have been distinctly modified by the removal of her sinus sepsis.

*Group 4 Chronic Atherosclerosis* A considerable number of patients with organic heart disease have an accompanying chronic sinus infection. Removal of the sinus infection in instances of rheumatic heart disease has not, in our experience, resulted in improvement of the patient's health. The

type of heart disease, however, spoken of by Benson<sup>2</sup> as atherosclerosis and by Clawson<sup>3</sup> as myocardial fibrosis, has been, in certain instances, remarkably bettered from a clinical standpoint by such treatment. The two patients noted herewith illustrate this point. Special note should be made of the extensive arterial fibrosis in the tissues removed from these sinuses (Figs 12 and 13). These vessel changes have not thus far been seen in the sinus membranes removed from other patients. They suggest a selective action for the blood vessels on the part of the micro-organisms present. These patients are especially apt to suffer coronary occlusion.

*Case 1* GC, age 62, June, 1929. The patient has suffered shortness of breath for six years, has been easily exhausted for the past four years, and worse the past month. He has had a chronic cough, non-productive most of the time, but periodically has had head discharge. His blood pressure has been elevated for at least two years. Shortness of breath has been the most distressing symptom. One flight of stairs must be taken very slowly, and then is accompanied by dyspnea and heart palpitation. For the past three years he has been considered primarily a cardiac case, and his life has been modified to meet this condition. Undoubted cardiac pathology exists. Electrocardiograms would indicate a right bundle branch block. The arch is widened, but the right heart is 3 cm and the left heart 9.8 cm, and the cardio-respiratory ratio is within 50 per cent. The absence of substernal dullness also points to the absence of failure. Because of the absence of cardiac failure the possibility of his chronic sepsis being the primary

cause of his illness was considered. Lipiodol roentgen films showed a general uniform thickening in both antra. On June 24th a double radical antrum, and a trans-antral ethmo-sphenoidectomy on both sides was performed. There was definite hyperplasia of all of the lining membranes without free pus. Cultures of the right antrum gave a few colonies of staphylococcus aureus, a moderate growth of the staphylococcus albus, a few beta hemolytic streptococci, and a heavy growth of a green-producing streptococcus. The left tissue gave a moderate growth of staphylococcus aureus, a few staphylococcus albus, occasional micrococcus catarrhalis, occasional hemolytic streptococci, and a heavy growth of a green-producing streptococcus.

Symptomatic recovery was very prompt. On the 7th of October, 1929, he reported feeling well. He had no dyspnea, no suggestion of heart trouble. His blood pressure was 144-76. Three months later he again made the same report.

*Case 2* RMW, age 59, May, 1927. The patient entered hospital with cardiac failure on the basis of the above cardiac pathology. Under hospital control it was found impossible to restore compensation. In the hope of obtaining compensation, it was decided to remove carefully all pus foci. June 1st tonsillectomy was performed and the patient had a stormy convalescence. The degree of his heart failure increased temporarily. On June 29th a double radical antrum operation was performed without much disturbance of the patient. Cultures from the left antrum gave a growth of slightly hemolytic streptococci and of non-hemolytic diplococci. Cultures from the right antrum gave a growth of non-hemolytic diplococci.

Following the removal of the infected tissue, compensation returned promptly and quite satisfactorily. For a year and a half he was in fairly good health. He returned to his business duties and also enjoyed fishing as a pastime. He died suddenly with a history of an acute coronary occlusion.

*Group 5* General Malaise. Many patients having a chronic sinusitis complain chiefly of merely being tired.

<sup>2</sup>BENSON, ROBT L. (The Present Status of Coronary Arterial Disease) Arch Path & Lab Med, Vol 2, Dec, 1926, pp 876-916.

<sup>3</sup>CLAWSON, B J. (Myocardium in Non-Infectious Myocardial Failure) Am J Med Sci, Vol CLXVIII, 5, Nov, 1924, p 648.

Often different etiological factors are found in such patients that could produce a general malaise, but in a certain number of them the sinus infection has proved to be of great importance

*Case 1* Mrs KH, age 54, September, 1929 This case illustrates a type of patient frequently encountered who complains for the most part of general malaise, weakness and nervousness, without the patient being of a general asthenic type of constitution, and with the presence of several etiological factors to consider For ten years the patient has had attacks of pain in the stomach and right upper quadrant She has been constipated, and has had much bloating and distress through the abdomen For years she has had frequent head colds with considerable post-nasal drainage For the past 2½ years she has been especially weak, tired, and nervous Examination showed a chronic hyperplastic sinusitis, chronic cholecystitis with stones, a spastic type of colon constipation, and a moderate grade of secondary anemia

Under control in the hospital it was found possible to regulate the bowel and relieve the motor disturbance at the end of the stomach incident to the gallbladder disease, but she did not feel especially better It was therefore decided that the chronic sinusitis was of more importance than the gallbladder disease, and on September 24, 1929, a trans-antral ethmo-sphenoidectomy on both sides was performed There was well marked hyperplasia of both antra, slight sphenoid and ethmoid thickening Cultures from the antra showed, from the left, gram positive alpha hemolytic streptococci, and a few colonies of staphylococcus albus, from the right a few colonies of alpha hemolytic streptococci, a few colonies of staphylococcus albus and a few colonies of micrococcus catarrhalis

A general improvement in the patient's health took place quite promptly following the operation, and the regulation of the bowel by means of a smooth diet continues to give her relief from the gastrointestinal distress

*Group 6* Neurologic Group An infectious cause for the so-called motility disorders, spasmodic tic, torticollis, chorea, epidemic hiccup, periodic hyperpnea, has gained credence in the last few years The work of Rosenow has been of special importance in this field Whether these disorders will ultimately be linked with encephalitis lethargica remains as yet problematical, but there are many suggestive facts being noted, which suggest a close relationship, as individual cases are being more closely studied The following three cases of tic, for instance, may well be removed from a psychogenic origin and be given an infectious cause In the entire group of cases listed herewith the seemingly important micro-organism found in culture has been a pleomorphic non-hemolytic faintly green-producing streptococcus which, nearly always in brain tissue and often in the tissues removed from the sinuses, seemingly exists as a diplococcus These clinical cases which have been, without reasonable doubt, linked with the associated sinus disease—offer to the problem of encephalitis lethargica at least the suggestion of a new approach for study

*Case 1* DB, age 9, December, 1929—Chorea The child developed a mild chorea about a week ago that has extended to the loss of control of the right hand and arm and the right leg and foot Aside from restlessness he is otherwise quite well In 1927 his tonsils were removed A month ago he had a head cold with fever and much post-nasal drainage He has had more or less discharge from his head for a long time A question of diplopia arose in September while the child was in school He complained of seeing double from time to time Examination revealed a soft systolic mitral murmur without evidence of cardiac failure,

and general thickening of both right and left antrums with polyp formation. Double radical antrum operation performed on December 10th, removed a thickened polypoid membrane from the left antrum, which also contained free pus, and a moderately thickened membrane from the right antrum.

Cultures from the tissues showed many colonies of alpha hemolytic streptococci, a few colonies of gram positive slightly hemolytic diplococci, and a few colonies of beta hemolytic streptococci, and of staphylococcus albus. A rabbit inoculated intracranially began to show, in 24 hours, definite choreiform movements. It was unable to walk, and seemed particularly unable to control its right side. Slight irritation of any part of its body produced a definite spasm. It died in 36 hours. Autopsy showed increased fluid in the knees, wrists, right hip and right elbow joints, there were inflammatory changes in the heart and the brain showed definite encephalitis. Cultures from these organs gave numerous colonies of alpha hemolytic streptococci, a few of beta hemolytic streptococci, and a few of a gram positive diplococcus. Grossly the brain and meninges were edematous, the cerebral vessels engorged with blood, the substance of the brain soft and friable but there was no purulent exudate. Microscopic sections revealed edema and hyperemia. The meninges were thickened and contained enlarged endothelial cells, with occasional polymorphonuclear leukocytes and spindle cells in the tissue spaces. Some areas of the cortex were soft and necrotic. There was no evidence of leukocytes within the brain tissue. The Lillie modification of the gram stain showed gram positive diplococci in the areas of cortical softening and in the perivascular tissues of the meninges. The heart and kidney showed parenchymatous degeneration. In another rabbit injected intravenously, the brain was edematous and hyperemic, but the tissue was firm; there was no evidence of softening, and bacteria were not found in the brain tissue, the cultures of the brain remained negative.

The boy is still in bed because of his endocarditis. All choreiform movements ceased soon after operation.

*\*Case 2* PS, boy age 14, August, 1928—Tic. The first appearance of the child's tic followed a prolonged sinus infection at the age of 6. From that time until his sinus operation September 12, 1928, there had been many recurrent sinus infections, always followed by exacerbation of the tic. Lessening of the intensity of the infection was correspondingly accompanied by an improvement in the patient's general physical condition and a lessening of the severity of the tic. Some months before his operation he had a subacute flare up of the sinus infection that was accompanied by a severe return of the muscle spasms. His early sinus infections were purulent. During the final flare up no pus was seen, and the radiographs were indefinite, showing only a suspicion of thickening. Three antrum punctures, at weekly intervals, gave no macroscopic pus, but polymorphonuclear cells were always seen in the cytologic examination. A double radical antrum operation was done. This revealed a soft, uniform thickening of the linings without surface discharge.

Recovery has been very gratifying. The whole physical and mental development of the boy has improved markedly, and now he has but an occasional twitch of any of the previously involved muscles. He appears to be quite a normal boy.

Swabs and tissues from the right antrum gave a growth of staphylococcus albus and green-producing short chain streptococcus. Cultures from the left antrum gave a growth of staphylococcus albus, micrococcus catarrhalis, and a green-producing streptococcus.

*Case 3* ER, boy age 14, November, 1928—Tic. Multiple tics began with acute onset without apparent cause six months before examination. Infected tonsils and purulent antral and ethmoid infection were determined. The tonsils and adenoids were removed with no improvement following. Double radical antrum operation was performed December 17, 1928. Definite thick-

*\*Cases 2, 3 and 4* were studied by our associate Dr. Selling, and have been reported in detail (Arch. Neurol. & Psych.) Dec., 1929, Vol. 22, pp. 1163-1171.

cning of the lining membrane with polypoid edema and some fibrosis was found

Following the antrum operation there was a reduction in frequency and intensity of the movements, but at the end of two months, the improvement not having been satisfactory, exenteration of the ethmoids and sphenoid sinuses was done. The lining of these cells was hyperplastic throughout. Following this last procedure there has been a steady improvement. There are slight residual tic movements remaining, but the boy is almost normal.

**Case 4** HS, boy age 11, October, 1928—**Tic** Multiple tics began gradually between the age of six and eight years, and became so pronounced at the age of ten that it was difficult for the boy to remain in school because of his jerking, twitching, and explosive speech. In his eleventh year he had violent attacks during which he became uncontrollable. Tonsillectomy had been previously performed without results. Radiographic evidence of chronic antrum disease justified exploration of the antra. The right antrum showed a moderate thickening and edema, and the lining contained three cysts. The left antrum showed definite hyperplasia in the alveolar recess. The rest of the lining showed very little change.

Very striking improvement followed the operation, but there continued to be periodic and at times severe recurrences of his tic for a period of three months. Since then, however, they have practically disappeared and the boy is considered quite normal at the present time.

Cultures from the left antrum contained a staphylococcus albus and micrococcus catarrhalis. Cultures from the right antrum gave a green-producing streptococcus.

**Case 5** Mrs HWQ, age 36, April, 1929—**Tic** Periodically recurring muscular twitchings, involving the legs, the arms, the neck and the head, began five years ago. During the early years the right side of the body was more affected than the left, but for the past two years the muscle spasms have been more severe on the left side. Septic tonsils were removed three years ago, without influence. Many devitalized, abscessed teeth have also been removed from

time to time without influence. The patient has had very little if any post-nasal drainage. Examination of the sinuses showed very little if any thickening of the right antrum membrane. The left antrum showed thickening with multiple polyps. A double radical antrum operation, and a trans-antral ethmoidectomy on the left side was performed May 18, 1929. A large cystic abscess in the left alveolar recess was found. The remainder of the antrum mucosa on both sides appeared to be thin. The left ethmoid and sphenoid membranes were also not appreciably thickened.

Swabs and cultures from the right and left antrum gave in cultures staphylococcus albus, green-producing streptococci and micrococcus catarrhalis. A rabbit inoculated with cultures of the tissues intravenously showed lesions in both hind joints and an irido-cyclitis of the left eye with conjunctivitis. Cultures of the heart's blood and of the anterior chamber of the eye gave green-producing streptococci. A second rabbit inoculated intracranially with 2 cc of the cultures of the tissues died in 48 hours. The brain was hyperemic with exudate and severe hemorrhage areas. Cultures of the brain gave a growth of green-producing streptococci. This rabbit developed definite muscular spasm to the left, as shown by the moving picture film. Microscopic examination of the brain of rabbit #2 showed a round cell infiltration of the meninges, noted in dense formation about the blood vessels that dip down into the brain substance. Some polymorphonuclear leukocytes and eosinophiles were present.

The patient's subsequent history has been most instructive. There was a complete subsidence of the tic during the period of surgical convalescence, that is, for a period of two or three weeks. During this time a vaccine prepared from the cultures obtained from the brain of rabbit #2 was given to the patient to see whether there would be any reaction from its use. The dosage was stepped up and finally a dose of 5 cc produced a very slight reaction. But following the reaction the tic began to return slowly but progressively with increasing severity. After two weeks the spasms ceased and the patient returned to her home. As they re-



appeared again the vaccine was started in doses of 0001 cc. By mistake the doses were increased in amount, and the spasms returned with great violence, completely invaliding the patient. After these violent muscle spasms subsided, a dosage of 000001 cc was given, an amount which we found did not produce a negative phase reaction.

For the past four months the patient has continued to take this dose of vaccine once a week, and had become nearly free from all manifestations of the tic for two months, but recently slight negative phase reactions returned and the dosage has again been reduced to a point where no reaction occurs. The patient remains in good health.

*Case 6* PA, age 27, logger, January, 1929—Torticollis and Tic. The patient was thrown, fifteen months ago while at work in the woods, and fell upon his back. At the time he did not seem to be bothered much and continued to work for two weeks. His head began then to draw spasmodically backwards to the right, the chin pointing to the left and upwards, and he suffered much pain. Spasms recurred at intervals of one-half to two or three minutes. In this condition he was examined by Dr. Selling, on the above date. His case was considered that of an organic torticollis, believing that in all probability there was a deep lying central lesion of a traumatic nature. At the same time a search for infections was made, with the result that infection of both antra was recognized. The possibility of the trauma having lowered the resistance of the brain structure so that this infection, (which before had been latent) could have produced focal brain lesions, was considered. The situation was explained to the patient, and, merely as a long chance, a double radical antrum operation, and a trans-antral ethmoid-sphenoidectomy on both sides was performed. There was much polypoid thickening of the alveolar recess of the right antrum, and moderate edematous changes in the left antrum. Both anterior ethmoid and sphenoid linings showed but a moderate thickening.

Very gratifying results followed the operation. In May, 1929, the backward pulling of the neck was very slight. He had

been at work. He can hold his head down and move it from side to side, but there is still some tendency for it to turn to the right. Later reports have indicated a very good end result.

Swabs and tissues from both antra in culture gave a growth of green-producing streptococci and a few staphylococcus albus. A rabbit injected intracranially with 2 cc of the tissue cultures, showed after 48 hours, tremors of the head, which was held backwards. It could move its forelegs but could not stand on them, and at times sprawled on all four legs. Autopsy showed a profuse hemorrhage and hyperemia of the brain and meninges. Cultures of the brain gave a greenish producing streptococcus.

*Case 7* Mrs FFW, age 51, January, 1927—Periodic Hyperpnoea. Periodic spells of distinct hyperpnoea, often accompanied with syncope, began 25 years ago. For several years the patient had repeated attacks. A second pregnancy did not influence the spells. The attacks came in very irregular intervals, day or night, but the patient always awakened at night during the early part of the period of hyperpnea. The attacks later subsided in frequency and severity until about six months ago when they became again very severe and very frequent. Complete neurological examination gave no important findings. Examination of the nose and throat showed an extensive atrophic rhinitis present on both sides, with almost complete loss of the inferior and middle turbinates. There was much discharge and crusting in the nose and pharynx.

Cultures from the washings of the antra in brain broth media gave a growth of a gram positive diplo-streptococcus. 4 cc of this culture was injected intracranially into a rabbit which died 24 hours later. Autopsy showed hemorrhagic areas in the brain and softening in the medulla. Cultures from the medulla contained a non-hemolytic gram positive diplococcus. A similar organism was obtained from one hind joint, which showed a slight increase in the amount of fluid. Several devitalized abscessed teeth were removed and cultures showed a non-hemolytic green-producing streptococcus with a few diplococci. A rabbit inoculated intra-

venously with 4 cc of this culture at autopsy revealed a joint lesion in the front leg from which a non-hemolytic streptococcus was recovered. The brain cultures were negative.

Because of the extensive atrophy, the patient was directed to douche the nose daily and use a lubricant. There was no operative work performed, although the margins of both antra were markedly thickened in the roentgen films.

The use of a vaccine prepared from the brain cultures in a dosage of 0.1 cc was used weekly until the following September, without recurrence of any attacks. In December, following what the patient thought was an acute food upset, she had three more attacks, two light ones and one severe one. She again resumed the use of the vaccine for a time. She has used none for the past 14 months. She continues the daily douching of her nose and at present remains well.

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We gratefully acknowledge our indebtedness to the members of the department of pathology for their assistance in this work, especially to Mr. Herman Semenov—Fellow in Pathology—for the histological preparations and his constant help in many ways.

lesions resembled those of a plasmodian infestation. Gregoire et al<sup>9</sup> reported a case in which the spleen was loaded with mycelial threads and spores. The organism of malaria has also been proposed and the possible syphilitic nature of the disease has been repeatedly indicated. The very variety of these supposedly etiologic agents suggests at once that none is the true cause.

*Metabolic and infectious toxins* have been given the causative role in the symptom complex, not only for the splenic enlargement but the same or a secondary toxin developed in spleen has been supposed to give rise to the cirrhosis. That hepatic cirrhosis is on a toxic basis may be true but this does not enter the scope of this paper. The claims for intoxication as the cause of the original splenomegaly are so vague and indefinite that we feel they can be definitely disregarded.

*Mechanical Interference* with the portal circulation or splenic venous flow is probably the most important factor. Many observations demonstrate the fact that the whole picture of "Banti's disease," aside from the cirrhosis, may be produced by a variety of gross mechanical lesions of the portal system. The more striking of these are (a) thrombosis of splenic or portal veins, (Klemperer<sup>10</sup>, Rosenthal<sup>11</sup>, Goldmann<sup>12</sup>, Warthin<sup>18</sup>, Mallory<sup>13</sup>), (b) stenosis of splenic vein (Leon-Kindberg<sup>4</sup> from Nancrede); (c) obstruction from pressure from without—gall-stone impacted in common duct (Armstrong<sup>14</sup> from Mayo, W.); and (d) congenital narrowing of portal bed in liver with patent umbilical

vein and portal vein hypertension (Moschovitz<sup>15</sup>—four cases from the literature). Cirrhosis of liver, portal of biliary has been suggested by many as the cause of the portal obstruction (Rolleston<sup>2</sup> from Naunyn, Gilbert and Lereboullet<sup>16</sup>, Dürer<sup>17</sup>, Klemperer<sup>10</sup>).

Warthin<sup>18</sup> tried the effect of ligation of the splenic vein in dogs and rabbits. He observed a moderate splenic enlargement followed in a number of weeks by atrophy. Such sudden cessation of flow in the splenic vein is not comparable to the slower occlusions of disease. One might draw an analogy. Ligation of a ureter gives rise to slight hydronephrosis followed by renal atrophy. But if the occlusion is slow, partial, or intermittent great degrees of hydronephrosis develop. Warthin himself recognized that his experimental results were misleading and concluded in spite of them that portal or splenic vein obstruction does produce the splenic lesions of "Banti's disease."

*Cirrhosis as a Cause.* Most of the above mentioned lesions produce portal obstruction in a more or less obvious fashion but the vascular changes in liver associated with cirrhosis need further consideration. It is apparent to anyone who has studied sections of frankly cirrhotic livers that there is indeed a reduction in size of the portal vessels throughout and that if the same volume of blood is to pass through the liver as through a normal one it must do so under a greater pressure. But even in a liver without patent scarring recognized as cirrhosis one may have definite narrowing of the vascular bed. Attention was called to this by Gilbert and Lereboullet<sup>16</sup> who demonstrated,

in cases of splenomegaly with little or even no gross evidence of cirrhosis a productive, fibroblastic reaction about the fine biliary passages with compression not only of the duct lumen but also of the adjacent vessels of the portal sheath, especially the venule. They believed these to be evidence of unrecognized biliary tract infection and were able in some of their patients to obtain a history of previous temporary illness with jaundice.

Anatomically, of course, interference with splenic circulation by changes in the liver is possible since the portal and splenic veins are entirely devoid of valves. The lesions in spleen look like the result of long standing passive congestion, the development of collateral circulation with esophageal varices, gastric hemorrhage and early ascites are also signs of portal obstruction. The secondary anemia is usually the result of gastric hemorrhage, gross or occult, but even without the latter a similar anemia is found in pure cirrhosis and in splenomegalies the result of gross portal obstruction.

*Purpose of Present Study* With this background in mind it is the purpose of the remaining part of this paper to report an attempt to measure, in a group of normals, a group diagnosed portal cirrhosis, and a group diagnosed "Banti's disease," the relative size of the hepatic portal radicals. The points to be studied were (a) the approximate quantitative narrowing of the vessels in cirrhosis and in "Banti's disease", and (b) the relation of the degree of narrowing to the size of the spleen, the age of the patient, and the degree of cirrhosis.

*Material and Methods* The material for study consisted of the routine liver sections of autopsies from the files of two large general hospitals, over approximately a 20-year period. Ten normals were selected from young individuals (15 to 30 years) who had died of acute infections. In doing this it was realized that the toxic changes in spleen make the weight of this organ of no significance to this study, but the establishment of a normal for portal vessels was all that was desired. Comparative studies of age and splenic weight were carried out only in the cases of cirrhosis and "Banti's disease." 23 cases in which the principal diagnosis of portal cirrhosis had been made and 4 cases diagnosed "Banti's disease" were used. A fifth case called "Banti's disease" showed great quantities of hemosiderin in liver and spleen. This case was omitted from the study because the effect of possible extraneous toxic factors on the organs (perhaps chronic copper poisoning) could not be excluded. The fact that most authors describe "Banti's disease" as occurring without pigmentation eliminates the case in the eyes of the majority.

Camera lucida tracings of the lumina of veins of the terminal portal sheaths were made, together with those of the immediately accompanying hepatic arterioles. The tissue was approximately from the same liver areas, namely just beneath the capsule, as is routinely taken in autopsy blocks. The cases were measured without knowledge of the diagnosis at the time of observation. The same microscope and camera lucida, with a constant tube length, side arm length, and mir-

ror angle were used, and all the tracings were made by the same individual. Actual calculation of the magnification was therefore unnecessary since all of them were on the same scale. A high power objective was used. In the normals there was no difficulty, but in the cirrhotic livers many vessels of the same type were found in the same mass of connective tissue, probably representing the remains of several collapsed lobules. For this reason careful selection was necessary to be sure that only the arteriole belonging to the venule chosen was traced. Occasionally in both normal and abnormal livers the portal radical was accompanied directly by two or rarely three arterioles. When this was absolutely certain the sum of the arteriolar measurements was used. The large number of small vessels of no particular structure, which represent the remains of liver sinusoids or new formed capillaries in the chronic inflammatory tissue, were avoided. Moreover only vein and artery in practical cross section or in almost exactly the same degree of oblique section could be utilized in order to obtain comparable figures. This again limited the number of observations possible on the two to five routine liver sections available in each case. Broken parts of the sections and branching vessels also could not be used. The number of suitable pairs of vessels for each case varied from 3 to 12, averaging about 6. On the normals a total of 59 tracings were made; on the cirrhosis 139, and on the Banti's 26. It was decided because of a degree of infolding present in many of the veins and some of the arteries, to measure the circumference of the

tracing of the vessel lumen rather than its diameter, although the work of Gilbert and Lereboullet<sup>16</sup> indicates that all of this infolding may not be artefact. Since absolute cross section was not possible the size of the vein was estimated in relation to the size of the artery rather than making a direct comparison of the size of the veins themselves. Thus the measurements represent an estimate of the relative size of the arterial and portal blood vascular beds in the liver.

It will be easily seen that many errors must necessarily be present in such a study but these have been reduced to the minimum by careful selection, the use of proportionate rather than absolute sizes, and the fact that such errors are more or less constant ones throughout. The average ratio in each case of arterial lumen circumference to vein lumen circumference (Ha-Pv ratio) was calculated and recorded and the average of this ratio was put down for each group, as seen in the tables. In addition there was noted the number of observations, age of the patient, weight of the spleen and an estimate of the amount of microscopic fibrosis in the liver. The weights were reported in grams. The tracing measurements were made in inches, but of course measurements by any other scale would give figures of exactly the same relative value.

The cases were grouped as follows: Table I, normals; Tables II and III, cases with the primary diagnosis of portal cirrhosis; and Table IV those definitely called "Banti's disease." The cirrhoses have been divided, more or less arbitrarily, into two groups, those without obvious splenomegaly, (Table

II, spleens less than 300 gms ) and those with definite splenomegaly (Table III, spleens from 300 to 805 gms ) The latter group forms an intermediate one between those in which cirrhosis dominates the picture and those in which the splenomegaly is the prominent feature The cases have been arranged in each table according to the weight of the spleen

### RESULTS

(1) *Spleen* Examination of spleens of the intermediate group showed in varying degrees the picture described by Banti There were some with perisplenic adhesions, all showed fibrosis, most of them had sclerosis of the adventitia of the Malpighian vessels, and many showed engorgement and sinus dilatation A number of them showed capsular thickening and sub-capsular fibrosis The spleens in the cases of frank cirrhosis often showed fibrotic changes The spleens of the "Banti's disease" group showed the histologic

changes supposed to be characteristic of this condition

(2) *Degree of Cirrhosis* It is apparent from the tables that the degree of hepatic fibrosis bears relation neither to the size of spleen, age of patient nor to the hepatic artery-portal vein ratio Whatever constricts or reduces the size of the portal venules is experimentally as well as theoretically not simply the compression of contracting scar, since as much or more reduction is noted in

TABLE I—NORMALS

Number	Observations	Age	Ha -Pv Ratio
(1) M-54-29	5	35	1-4 6
(2) M-47-29	5	30	1-3 4
(3) M-71-29	7	30	1-7 3
(4) M-72-29	5	28	1-7 9
(5) M-56-29	6	28	1-8 2
(6) M-70-29	7	24	1-5 4
(7) M-61-29	6	21	1-8 4
(8) M-75-29	5	20	1-4 5
(9) M-76-29	6	19	1-5 1
(10) M-51-29	7	15	1-6 2
Average of	59 obs	25	1-6 0

TABLE II—CIRRHOSIS—SPLEEN LESS THAN 300 GMS

Number	Obs	Age	Degree Cirrhosis	Wt of Spleen	Ha -Pv Ratio
(1) A-26-21	3	40	Moderate	275	1-5 2
(2) A-31-23	8	40	Mild	240	1-5 0
(3) A-19-29	6	47	Severe	220	1-5 8
(4) A-35-27	5	64	Mild	205	1-5 6
(5) M-40-25	5	72	Mild	175	1-3 9
(6) M-74-22	4	64	Severe	165	1-3 2
(7) A-7-28	5	64	Mild	155	1-5 4
(8) M-30-29	6	66	Severe	155	1-3 1
(9) M-33-23	4	55	Moderate	120	1-3 8
(10) A-6-28	7	65	Severe	100	1-2 5
(11) A-20-25	6	70	Severe	95	1-3 4
(12) M-9-27	5	65	Moderate	80	1-4 7
Average of	64 obs	59		165	1-4 3

Approximate reduction of vascular capacity in liver 29%

TABLE III—CIRRHOSIS—SPLEEN MORE THAN 300 GMS

Number	Obs.	Age	Degree Cirrhosis	Wt of Spleen	Ha -Pv Ratio
(1) M-12-30	11	45	Severe	805	1-2 3
(2) A-2-23	3	39	Moderate	645	1-4 3
(3) A-70-28	9	41	Severe	625	1-2 6
(4) M-63-28	4	33	Severe	600	1-4 4
(5) M-62-22	7	44	Severe	525	1-2.1
(6) M-43-29	7	46	Severe	380	1-2 8
(7) M-5-30	10	44	Mild	375	1-3 7
(8) A-13-28	5	73	Moderate	335	1-4 1
(9) A-24-29	8	52	Severe	330	1-4 0
(10) M-28-23	4	75	Moderate	300	1-3 3
(11) A-65-24	7	62	Mild	300	1-4 2
Average of	75 obs	50		475	1-3 4

Approximate reduction of vascular capacity in liver 43 5%

TABLE IV—CASES DIAGNOSED "BANTI'S DISEASE"

Number	Obs	Age	Degree	Wt of Spleen	Ha -Pv Ratio
(1) M-52-29	12	28	Severe	1300	1-2 8
(2) M-81-25	5	19	Mild	1000	1-2 4
(3) M-81-29	5	29	Severe	505	1-2 8
(4) M-11-22	4	46	Moderate	300	1-3 2
Average of	26 obs	30		776	1-2 8

Approximate reduction of vascular capacity in liver 53%

cases with little fibrosis as in those most extensively sclerosed. For instance it is seen that Case 2, Table IV, has an extremely large spleen and but little apparent evidence of cirrhosis. Yet the hepatic portal venules are greatly narrowed (ratio 1 to 2 8). Such a case might have been considered splenic anemia without cirrhosis and placed in the category of primary splenomegaly had not the measurements definitely indicated a vascular lesion in liver.

(3) *Age*. Age has apparently a definite effect on the amount of splenic enlargement. The average age in the

"Banti" group was 30 years, that of the intermediate group 50 years, and that of the cirrhotic group 59 years. If Tables II, III and IV were superimposed it would be apparent that, with a few exceptions, as age increased the amount of splenic enlargement decreased in all three groups. One can also see that the division into groups is an entirely artificial one, the one group overlapping and merging imperceptibly into the other in a continuous transition from frank cirrhosis through intermediate forms to the picture of "Banti's disease." Thus it looks as if the older the spleen the less able

it is to enlarge in response to back pressure and that perhaps the reason cirrhosis predominates in older individuals and splenomegaly in younger ones is simply that with the same degree of portal obstruction the young spleen enlarges to a much greater degree than the older one. Expressed mathematically then, the amount of splenic enlargement is roughly inversely proportionate to the age. Chart I shows the relationship graphically. The entire group has been arranged in order of age, and shows the rapid drop in splenic enlargement with increasing age. The effect is more marked in the earlier decades than in the later ones.

(4) *Narrowing of the Hepatic Vessels* Inspection of the tables shows a normal Ha-Vp ratio of 1 to 60 (Table I). The cirrhotics with little or no splenomegaly (Table II) showed a ratio of 1 to 43, a drop of 29% in the capacity of the portal vessels. The intermediate group, i.e. cirrhosis with

splenomegaly had an average ratio of 1 to 34, or a 43.5% reduction. The group diagnosed "Banti's disease" averaged 1 to 28, representing a 53% loss of normal vascular capacity in the hepatic portal radicals. Attention is called to the great regularity of excessive vascular narrowing in the latter group regardless of the degree of hepatic fibrosis. Again, reference to the tables shows that just as was the case with age, throughout all the groups there is a gradual merging so that the Ha-Vp ratio of cases of the intermediate group fall in at one end with the frank cirrhosis and at the other end with those of "Banti's disease." It is also seen that the size of the spleen is in general directly proportionate to the degree of capacity loss and inversely proportionate to the degree of available vascular bed. Chart II shows graphically the relationship of the size of the portal venules (Ha-Pv ratio) to the weight of the spleen.

Chart I.

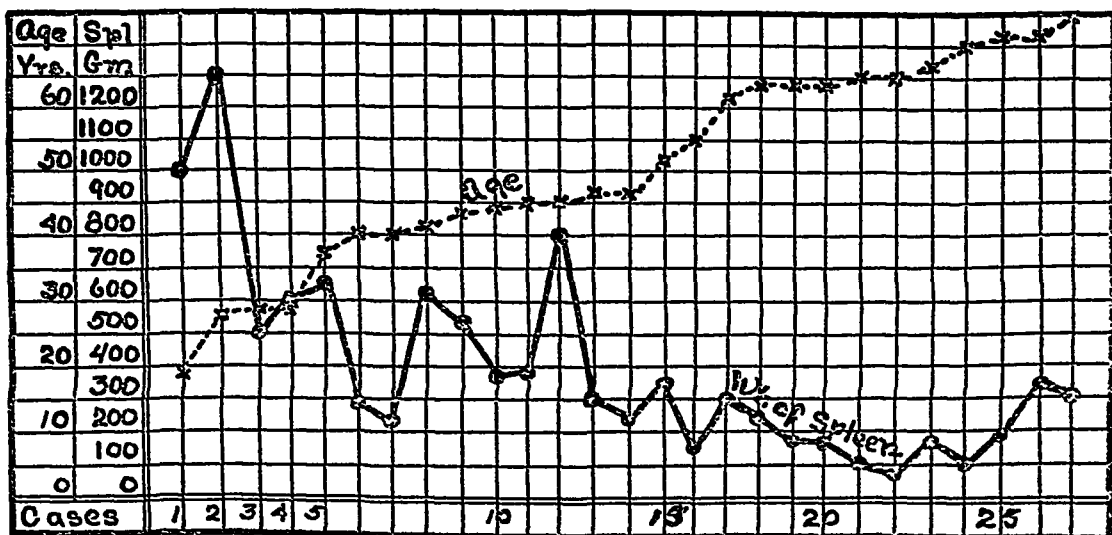


CHART I Shows the 27 cases of Cirrhosis and "Banti's Disease" arranged according to age. Note the marked decrease in Splenic enlargement with advancing age.



It shows the great *increase* in splenic enlargement with decrease in vessel size. Apparently a certain degree of narrowing (approximately 50%) can be compensated, after which the effect is much more pronounced. The percentage losses cited above seem quite large but probably do not represent as much reduction as occurs, since it represents merely the reduction in relation to the size of the arterioles, many of which are undoubtedly atrophic, and does not take into account possible pressure infolding. It must be admitted that a certain number of small vessels are found in the sclerosed portal sheaths which may represent new

formed vessels associated with the fibroblastic reaction, but these are so small that their resistance must be great and the formation of extensive collateral circulation easily shows that these are far from able to compensate for the loss of normal vascular area.

(5) *Relation of Age to Size of Vessels in Liver* Since the curves for age and Ha-Vp ratio are so similar it might be argued that the narrowing of vessels was simply the result of advancing age. Chart III, however, shows the relation of Ha-Pv. ratio to age in the normals and in those cases of "Banti's disease" and cirrhosis falling in the same age range. It is readily

Chart II.

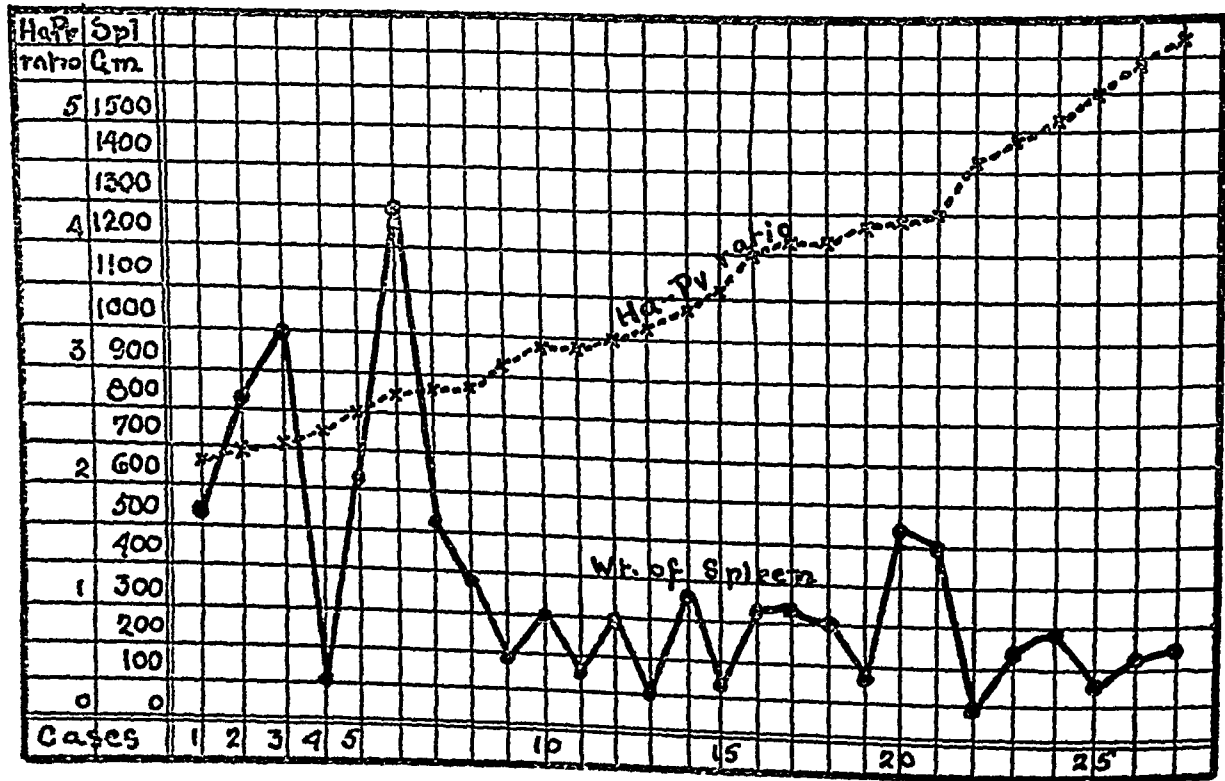


CHART II. Shows the 27 cases of Cirrhosis and "Banti's Disease" arranged according to the Ha-Pv ratio (ratio of circumference of hepatic arterioles to portal venules in the same portal sheaths). Note the marked splenic enlargement in the cases with greatly contracted portal venules (ratios of less than 1-30, i.e., half the normal ratio of 1-60). Case 4, an exception, was 65 years old and no doubt age was a strong factor in preventing splenic enlargement.

seen, even though the number is small, that the hepatic portal radicals are much smaller at the same age in the pathologic cases than in the normal ones

### SUMMARY AND CONCLUSIONS

In conclusion we may say that both from the observations cited in the literature and from our own results there is strong evidence that in those

conditions known as splenic anemia and "Banti's disease" we are dealing with mechanical alterations of the portal blood flow interfering with the free exit of blood from the spleen. The more important lesions bringing this about may be summarized as follows

#### I Congenital anomalies

- I Patent umbilical vein with excessive portal flow

### Chart III.

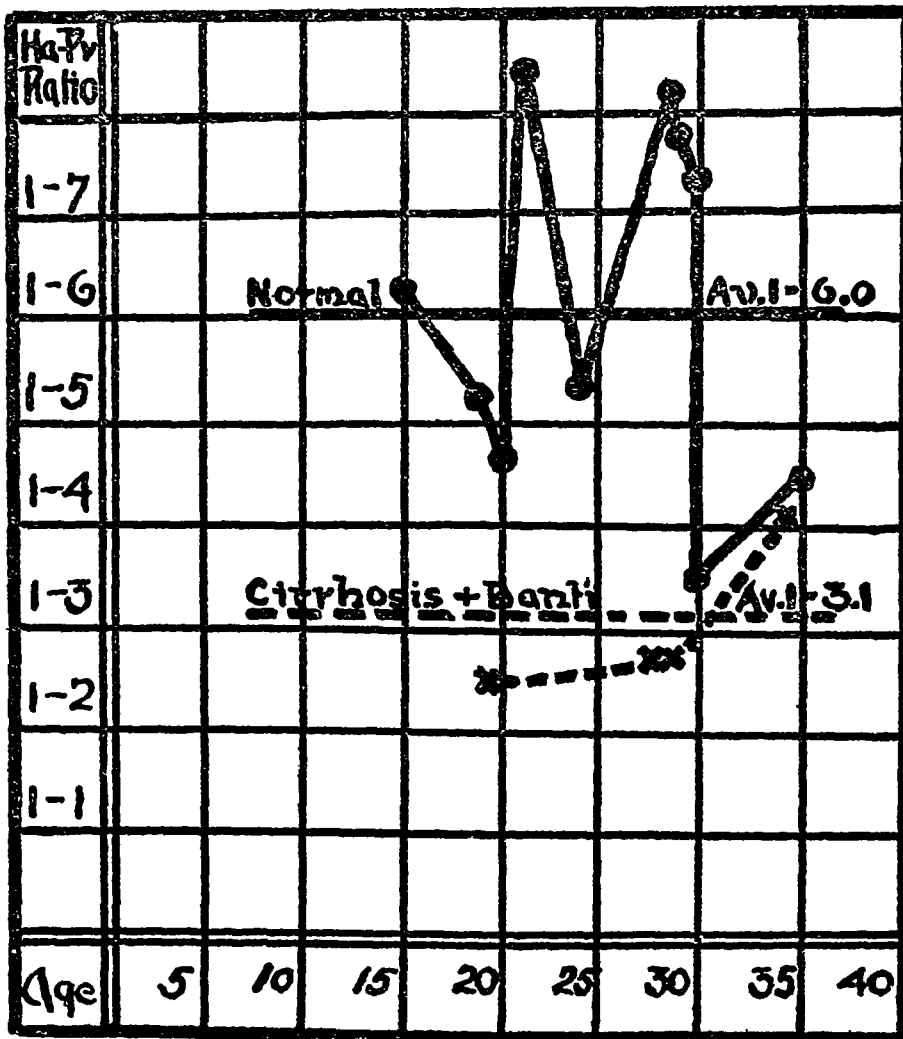


CHART III Shows the relation of Ha-Pv ratio to age in the normals and in those cases of Cirrhosis and "Banti's Disease" which fell in the same age range. Note that the Ha-Pv ratio in the pathologic group falls far below the normals, so that vessel narrowing in liver is not merely a function of age

It shows the great *increase* in splenic enlargement with decrease in vessel size. Apparently a certain degree of narrowing (approximately 50%) can be compensated, after which the effect is much more pronounced. The percentage losses cited above seem quite large but probably do not represent as much reduction as occurs, since it represents merely the reduction in relation to the size of the arterioles, many of which are undoubtedly atrophic, and does not take into account possible pressure infolding. It must be admitted that a certain number of small vessels are found in the sclerosed portal sheaths which may represent new

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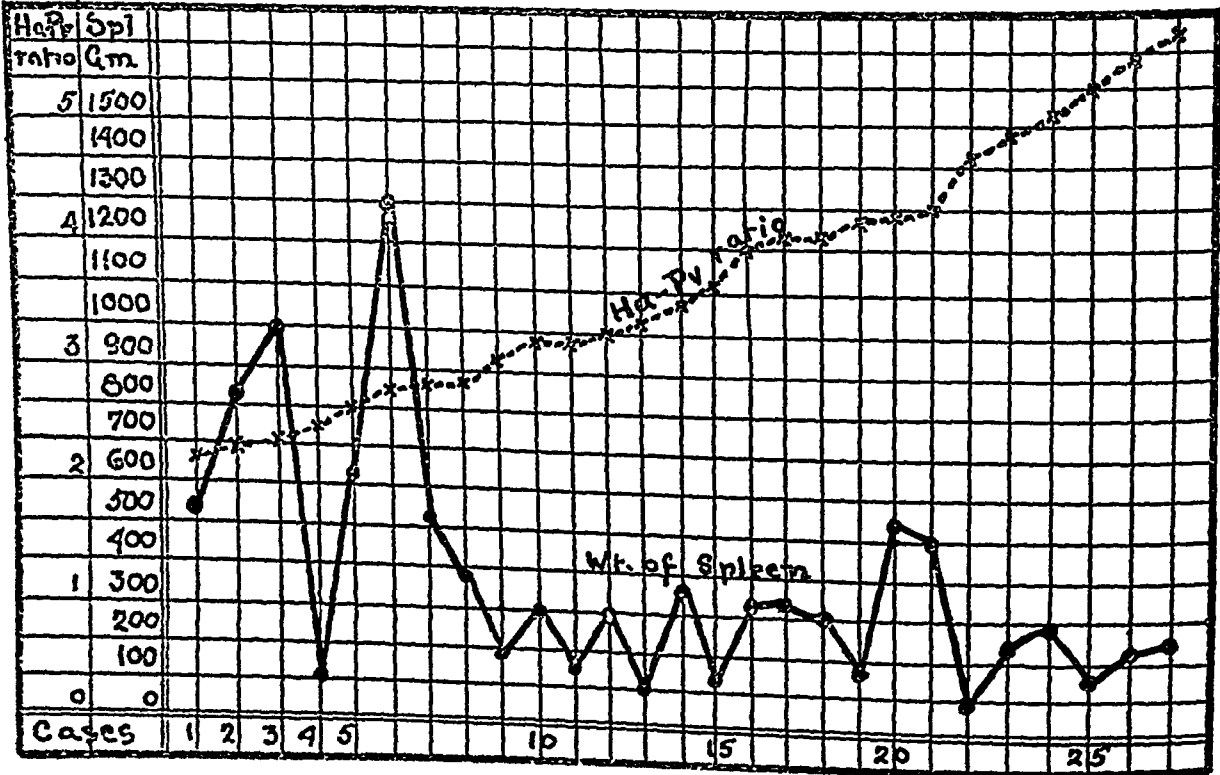


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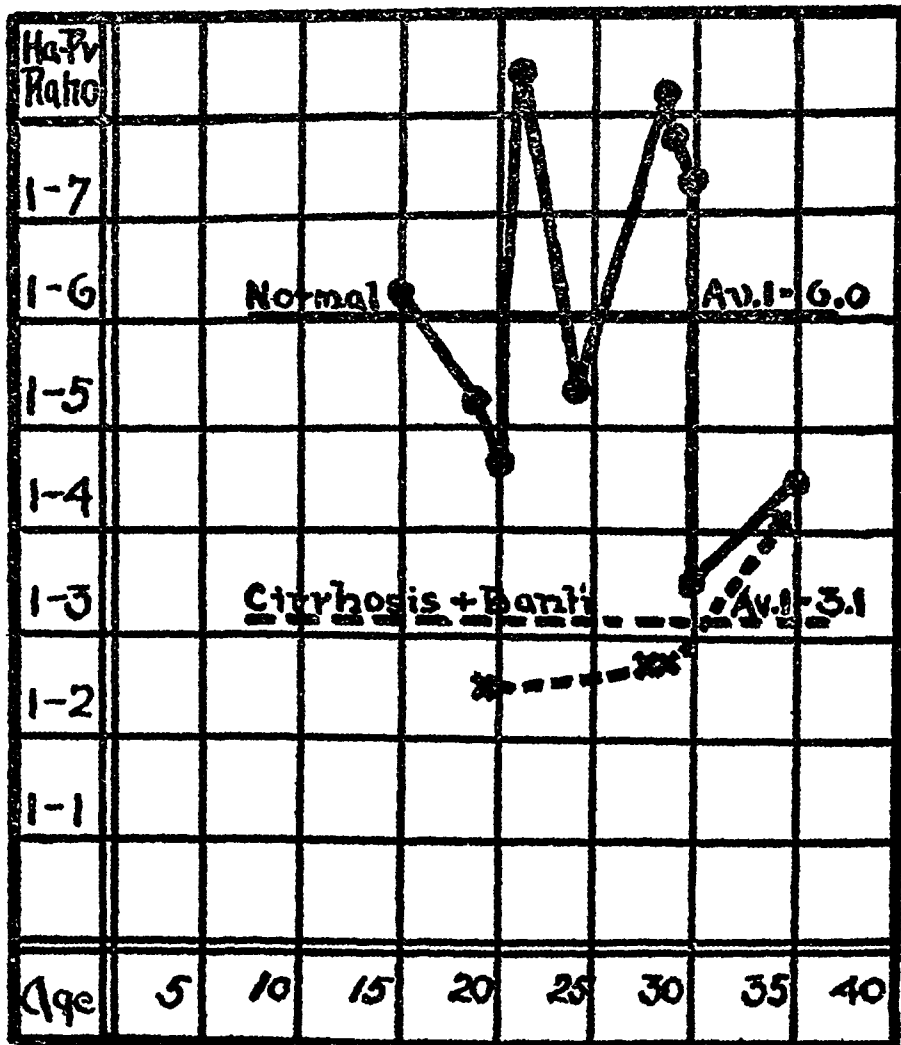


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- 2 Hypoplasia of liver or of portal veins in liver
3. Narrowings or distortions of lumina of vessels

II Pressure from without on portal or splenic vein by calculus, tumor or adhesions.

III Cirrhosis of liver.

IV. Thrombosis of portal or splenic vein

It is obvious that these changes do not always produce a picture in which the splenomegaly predominates. Other factors are present. Probably the most important of these is age; the younger individuals responding with a greater degree of splenic enlargement than the older ones. In the cases associated with cirrhosis the factor of importance is not the fibrosis present *but the degree of vascular narrowing*, which as

we have seen can be extreme even when there is little if any gross fibrotic reaction and even when there is little microscopic scarring. We do not know what causes the vascular narrowing or even the cirrhosis. If toxic, it may come from the bowel or stomach as readily as from the spleen. One undoubtedly sees clinically the syndrome of "Banti's disease" but that this is a primary splenomegaly with secondary cirrhosis seems unfounded. The indications are that a number of pathological conditions, such as described, can give rise to this picture.

*Note* Thanks is expressed to Dr J A. Perrone for assistance in translations, to Dr S R Haythorn for the use of his sections and records, and to Dr H H Permar for his valuable suggestions and assistance in preparing this paper.

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# The Association of Cholecystitis With Cardiac Affections—A Study Based on 109 Cases\*

By MORRIS SCHWARTZ, M D  
and  
ALBERT HERMAN, M D, *Philadelphia*

INSTANCES in which infections of the gall bladder are complicated by affections of the heart are numerous and most physicians have had more or less experience with the association. It is well known that an existing cardiac affection may be greatly aggravated by a superimposed acute or chronic cholecystitis, and likewise the idea is gaining ground that a chronically diseased gall bladder may act as a focus of infection, initiating baneful changes upon organs and tissues unassociated with the gastrointestinal tract.

## LITERATURE

Tessier<sup>1</sup> in 1879 classified cardiac disturbances depending on gastro-hepatic diseases. Gueneau de Mussy<sup>2</sup> in 1878 stated that the cardiac murmur found in gall bladder disease was due to the paralyzing effect of bile salts upon the vasomotor and general circulatory system. Gangolphe<sup>3</sup> believed the principal effect upon the heart was on the papillary muscles, while Fabre<sup>4</sup> considered it a myocarditis due to the accumulation of bile salts in the blood.

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\*From the Medical Service of Dr A I Rubenstone, Mt Sinai Hospital, Philadelphia.

Leva<sup>5</sup> in 1892 reported from Eichorst's Clinic in Zurich, 2 cases of ulcerative endocarditis resulting from gall bladder disease. In 1893 Oddo<sup>6</sup> of Marseilles reported a case of pericarditis and arrhythmia, which developed two days after an attack of biliary colic. Riesman<sup>7</sup> in 1907 and again in 1911<sup>8</sup> reported cases in which during an attack of biliary colic there developed mitral systolic murmurs which were not present previously, and which disappeared after the subsidence of the pain. This he interpreted as due to temporary cardiac dilatation, due to strain and increased tension. Robert Babcock<sup>9</sup> in 1909 and also in 1919<sup>10</sup> reported cases in which the symptoms were mainly referable to the circulatory system. These cases after careful study proved to have coexisting cholecystitis and some were much improved after biliary tract surgery. Hoppe-Seyler<sup>11</sup>, Umber<sup>12</sup> and Kuller<sup>13</sup> in individual articles in the German literature comment on the relation of cardiac arrhythmias to gall stone colic. Lichty<sup>14</sup> in 1915, stated that while in appendicitis the cardiac disturbance was functional, in gall bladder disease the heart is more seriously affected. Sir Humphry Rolleston<sup>15</sup> in 1920 con-

firmed this view. Ransohoff<sup>16</sup> in 1924 stated that the association of cholecystitis and myocarditis was so common as to demand serious attention. Strauss and Hamburger<sup>17</sup>, Mayo<sup>18</sup> and others cite cases of myocarditis and various types of cardiac arrhythmias which were relieved or improved after surgical treatment of the biliary tract.

In the past two decades, therefore, and particularly since the monumental work on focal infection by Rosenow<sup>19</sup> in 1914, the infected gall bladder has been accused of being the primary focus for pathologic changes in many other organs, including the heart.

The foregoing citations from the literature as well as the experience of numerous practitioners, while showing that there often is an association of the two diseases, do not, however, indicate how frequently the combination occurs. From a practical standpoint it is important to know in what percentage of cases of cholecystitis, one may also expect to find an affected myocardium. As far as we have been able to ascertain, only two such studies have heretofore been carried out, the first by Willius and Fitzpatrick<sup>20</sup> of Rochester, Minn., in 1925, and the second by Leech<sup>21</sup> of Boston within the past year. They analyzed 596 and 116 cases respectively. Inasmuch as both these series deal with patients who presumably sought surgical intervention, and who probably had the more serious types of cholecystitis—of the first series 34% of all the cardiacs were operated upon, and the entire group of the second series had operations—it should be expected that more representative information might be obtained from a group studied in a medical service,

where the type, duration and severity of the disease would likely be more varied.

#### PRESENT STUDY

Our studies are based on 109 unselected cases of cholecystitis which were treated consecutively in the medical wards of Mt. Sinai Hospital since 1924.

The diagnosis of cholecystitis was made on the history, clinical findings and laboratory data which included x-ray studies, such as flat plate of the gall bladder area, cholecystography, duodenal drainage, icterus index and the Van den Bergh test. Frequently, to rule out other conditions, urologic studies including pyelography; pelvic examinations; x-ray of the lumbar spine and sacro-iliac regions; and gastro-intestinal x-ray studies were made.

The criteria for establishing a diagnosis of heart disease, consisted of a history of circulatory disturbance such as dyspnea, cough and so on; the presence of cardiac abnormalities as revealed by careful physical examination; blood pressure readings, and as required, orthodiagrams and electrocardiographic tracings.

There were 93 females and 16 males. The youngest patient was 21 years and the oldest 75 years. Chart 1 indicates the age distribution according to decades. Whilst children above the age of 12 were admitted on the medical service, there were no cases of cholecystitis before the age of 20. The greatest number of cases in a single decade numbered 31, and occurred in the fifth decade. The fourth, fifth and sixth decades totaled 79 or 72% of all the cases. There were 15 cases in the

third decade, and the seventh and eighth decades together numbered 15 cases—25 or 22.9% of these cases were calculous and 84 or 77.1% were non-calculous

#### ASSOCIATED DISEASES

Focal infection either in the form of diseased tonsils, chronic sinusitis, den-

tal caries, endocervicitis or mild prostatic disease occurred in 106 of the 109 cases Table 1 lists the most frequent associated conditions There were 69 patients (63%) with heart disease, 57 (52%) with obesity, 9 (8%) with diabetes, 7 (6%) with sacro-iliac disease, 5 (4%) with ureteral stricture and 3 cases with chronic pancreatitis

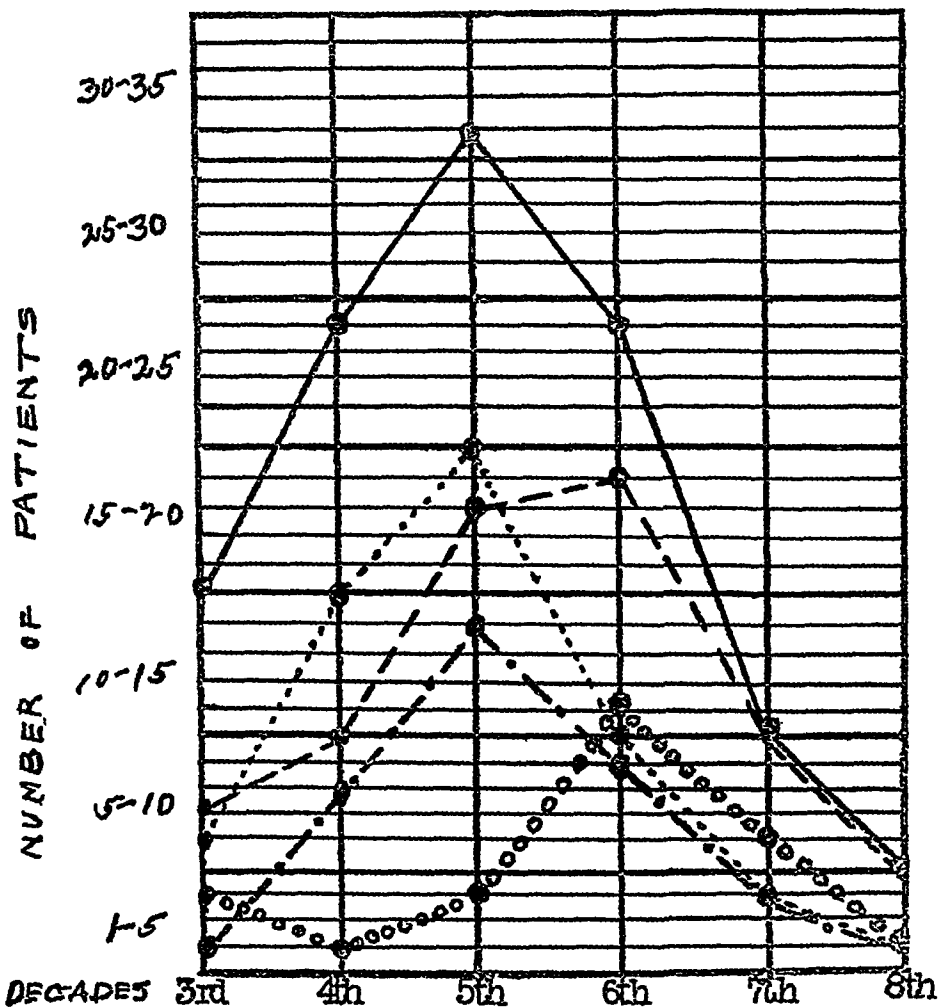


Chart 1 Showing the age in decades of 109 cases of cholecystitis, the number associated with obesity, the number associated with heart disease, comparing the fat with the lean

- Cholecystitis
- Cholecystitis with obesity
- ..... Cholecystitis with heart disease
- . - . - Cholecystitis with obesity and heart disease
- o o o o o Cholecystitis with heart disease, no obesity



TABLE 1

Showing the number and variety of associated conditions in 109 cases of cholecystitis

Heart Disease	69
Obesity	57
Diabetes	9
Sacro-iliac Disease	7
Ureteral Stricture	5
Pancreatitis With Questionable Malignancy	3
Chronic Appendicitis	3
Renal Calculus	3
Intercostal Neuralgia	3
Chronic Nephritis	3
Nephroptosis	3
Menopause	3
Spondylitis	2
Pelvic Inflammation	2
Miscellaneous	18

#### HEART DISEASE -

These totaled 69, and indicates that 63 3% of all the gall bladder cases had an associated cardiac condition. Chart 1 shows that the greatest number of heart cases occur in the fifth and sixth decades—18 and 19 respectively, the fourth and seventh decades each contain 10 cases. It will be noted that with advancing age the lines representing gall bladder disease and heart disease approximate each other closer and closer until they coincide in the seventh and eighth decades. Table 2

TABLE 2

Showing the percentage of heart disease in each decade. 109 cases of cholecystitis, 69 heart cases

3rd Decade	46 6%
4th Decade	41 6%
5th Decade	58 6%
6th Decade	79 1%
7th Decade	100 %
8th Decade	100 %

shows the increasing percentage of heart cases in each decade, beginning with 46 6% in the third decade and

ending with 100% in the seventh and eighth decades

#### OBESITY

There were 57 patients with gall bladder disease who, when judged by clinical standards, considering sex, age, height and weight, were found obese. This represents 52 2% of the entire group. A glance at Chart 1 shows that in contrast to the incidence of heart disease, which increases with the advancing age of the patient, obesity is most frequent during the age period between 30 and 50, totaling 35 or 61% of the entire obesity group. After the age of 50, the tendency to obesity is diminished, but remains at a constant level. Table 3 shows that 62% of all the gall bladder cases in the fourth decade and 64% of the fifth decade, have associated obesity, while in the other age periods it is 40%

TABLE 3

Showing the percentage of obesity in each decade. 109 cases of cholecystitis, 57 cases of obesity

3rd Decade	40 %
4th Decade	62 6%
5th Decade	64 5%
6th Decade	41 6%
7th Decade	40 %
8th Decade	40 %

#### OBESITY AND HEART DISEASE

In order to learn what relationship obesity had to myocardial changes of the cholecystitics, we tabulated the number and types of myocardial disease present in this group with particular reference to the age of the patients.

More than half of all the cardiacs (39 or 56 5%) were obese. This corresponds to over 68% of the obesity

cases Chart 1 shows graphically that the cardiacs with obesity follow the line of the general obesity group, but resemble the total heart group by having an increasing proportion of cardiacs as the age advances. The greatest number, however, occur in the fourth, fifth and sixth decades, totaling 31 cases or 79% of all the obese cardiacs. Table 4 shows the percentage of cardiacs per decade in the obesity group and compares it with the remaining non-obese cardiac cases. In comparing these two groups, one is at once struck with the fact that the chances of having heart disease in association with gall bladder infection are much greater in the fat than the lean, particularly in the fourth and fifth decades of life where it is at least twice as numerous, while after the sixth decade, the chances of having heart disease is about even in both groups. This is shown graphically in Chart 1.

TABLE 4

Comparing the percentage of heart disease per decade in the obese, and non-obese patients (57 obese patients, 39 cardiacs) (52 non-obese patients, 30 cardiacs)

	Non-Obese	Obese
3rd Decade	44.4%	33.3%
4th Decade	22.2%	53.3%
5th Decade	36.3%	70%
6th Decade	78.5%	90%
7th Decade	100%	100%
8th Decade	100%	100%

It will be noted that in the third decade the percentage of cardiacs in the obese group is somewhat less than in the non-obese, 33% against 44%. This may be explained by the observation of Master and Oppenheimer<sup>22</sup>, who found that moderate overweight in young patients is an advantage and

that they respond better to cardiac exercise tolerance tests than normal persons.

#### VARIETIES OF HEART DISEASE

In this series, we have failed to meet with cases of definite rheumatic or syphilitic heart disease. We have divided our cases into four groups:

- 1—Chronic myocardial disease
- 2—Hypertensive heart disease
- 3—Arteriosclerotic heart disease
- 4—Combined hypertensive and arterio-sclerotic heart disease

This grouping is perhaps open to criticism, but there can be no question in anyone's mind as to what is meant by the last three groups. In naming the first group chronic myocardial disease we have taken liberties with the classification of Christian<sup>23</sup> by excluding the evident arteriosclerotic and hypertensive cases. We use the term in the same sense that he does, however, implying that it represents a type of myocardial insufficiency for which no definite etiologic factors are evident. Furthermore, our study suggests that in cholecystitis this is the type of heart which predominates, and is probably caused by the combined action of the infected gall bladder plus obesity.

Table 5 shows the number of heart cases in each group, contrasting the obese with the non-obese. The greatest number belong to the group of chronic myocardial disease,—43 cases or over 62%. The rest comprise 26 cases. The first group is about equally divided between the obese and the non-obese, but the hypertensive and arterio-sclerotic types are about twice as frequent among the obese. Table 6 presents the

TABLE 5

Tabulating the number of cases in the various types of heart disease in the obese and non-obese

	Chronic Myo- card Dis	Hypert H D	Art Scl H D	Combined A S & Hypert	Total
Non-Obese	21	3	4	2	30 or 43 5%
Obese	22	7	6	4	39 or 56 5%
Total	43 or 62 2%	10 or 14 4%	10 or 14 4%	6 or 8%	69 or 100%

age groups for the various types of heart disease, showing that the hypertensive and arteriosclerotic types manifest themselves after the 40th year, coinciding with the usual age incidence for these types of heart disease

Chart 2 and Table 6 contrast the relative frequency of the cases with

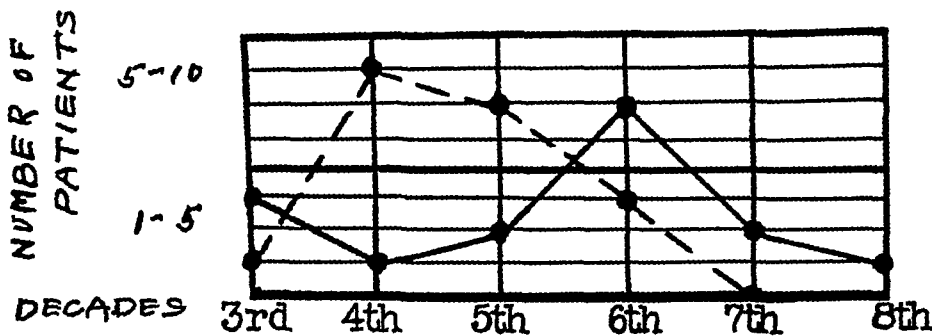


Chart 2 Showing the relative age of 43 cases of cholecystitis associated with chronic myocardial disease in the obese and non-obese  
- - - - Cholecystitis, myocardial disease and obesity  
———— Cholecystitis, myocardial disease, no obesity

TABLE 6

Tabulating the number of cases in each group of heart disease, with relation to age and obesity

		3rd Decade	4th Decade	5th Decade	6th Decade	7th Decade	8th Decade	Total
Chronic	Not							
Myocard	Obese	4	2	3	7	3	2	21
Dis	Obese	2	8	7	4	1		22
Hypert	Not							
H D	Obese				1	2		3
Art Scl	Obese			4	2	1		7
H D	Not							
Combined	Obese			1	1	1	1	4
Hypert	Obese			2	2	2		6
Art Scl	Not							
H D	Obese				2			2
	Obese			1	1		2	4

chronic myocardial disease in the obese and non-obese groups, and show quite definitely that in the fourth and fifth decades the obesity cases are far in the ascendency, while after the age of 50 the preponderating number of cases are in the non-obese group

#### RELATIVE FREQUENCY OF HEART DISEASE IN PATIENTS WITH CHOLECYSTITIS AND WITHOUT CHOLECYSTITIS

In an effort to determine with some degree of certainty whether and how much of a rôle cholecystitis plays in the causation of cardiac affections, we

chose at random 109 non-cholecystitic medical cases in identical age groups which were treated in the wards of the hospital, and contrasted the relative frequency of heart disease in this group with the gall bladder group. We excluded no cases except those which were cardiac per se, as rheumatic fever, subacute and acute endocarditis and so on.

Chart 3 and Table 7 shows that the non-gall bladder patients have a much less incidence of cardiac disease—41% as against 63% in the cholecystitics. The gall bladder heart cases almost double and quadruple the non-

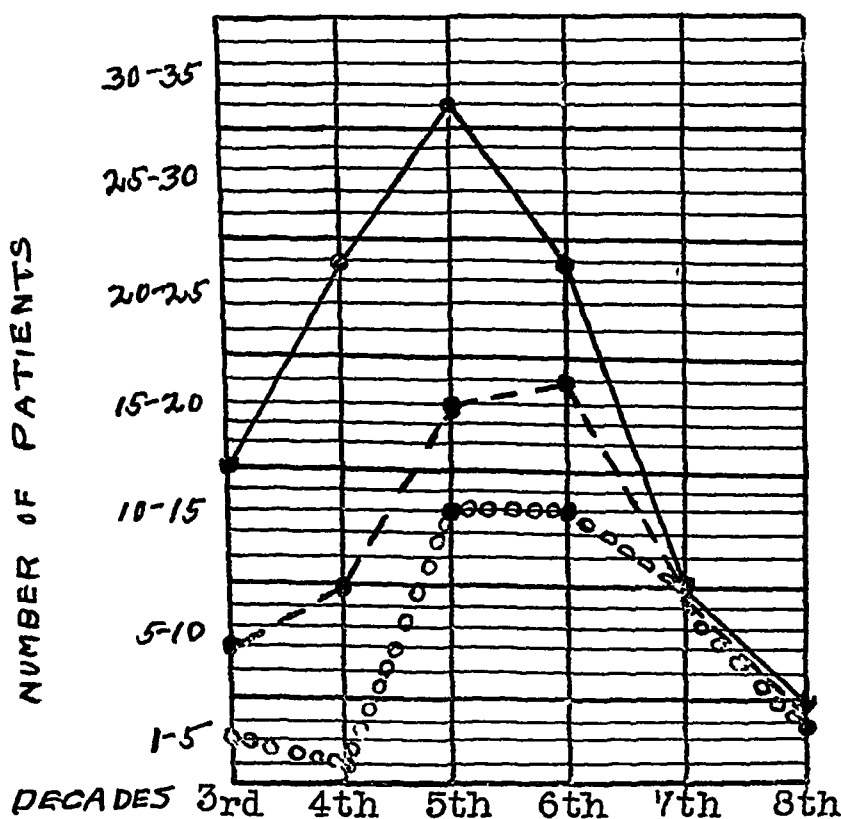


Chart 3 Contrasting the incidence of heart disease in 109 cholecystitics against 109 non-cholecystitics

69 cholecystitics with heart disease

45 non-cholecystitics with heart disease

———— Cholecystitics

- - - - Cholecystitics with heart disease

o o o o o Heart disease without cholecystitis

TABLE 7

Showing the percentage of heart disease per decade in 109 patients without cholecystitis, comparing it to 109 patients with cholecystitis and 52 non-obese patients with cholecystitis

	Non Gall B	Chole- cyst	G B with- out Obes
3rd Decade	20 %	46 6%	44 4%
4th Decade	8 %	41 6%	22 2%
5th Decade	41 9%	58 6%	36 3%
6th Decade	54 1%	79 1%	78 5%
7th Decade	100 %	100 %	100 %
8th Decade	80 %	100 %	100 %

gall bladder cases in the third and fourth decades respectively, with about 20% greater frequency in the fifth and sixth decades, but both groups are about even in the seventh and eighth decades. Lest it be assumed that the reason for the preponderating number of heart cases in the cholecystitic group is due to its associated obesity, we have appended the third column in Table 7 which consists of our non-obese gall bladder cases with cardiac affections. This latter group, in its percentage of heart cases also exceeds by a great margin, those individuals

who have no biliary disturbance. An exception is present in the fifth decade, in which there is a slight preponderance of heart cases in the non-cholecystitics.

#### THE RELATION OF THE SEVERITY OF CHOLECYSTITIS TO THE SEVERITY OF THE CARDIAC AFFECTIONS

Table 8 indicates that 44% of the 109 gall bladder cases belong to the severe group of cholecystitis as judged by biliary colic, jaundice and other clinical data. Well-marked heart disease, based on the finding of more than moderate hypertrophy, or electrocardiographic evidence of marked myocardial or coronary disease, or decompensation, numbered 49 or 71% of all the cardiacs. There was a total of 11 or 15.9% with decompensation. It will be noted that there was no apparent difference in the effect upon the heart in the mild or the severe cholecystitics. In order to determine the relative effect of mild or severe cholecystitis on the hearts of the younger individuals, we studied this relationship in the pa-

TABLE 8

Showing the relative frequency of clinically mild and severe cholecystitis with relation to moderate and well marked heart disease, and decompensation

	Total
60 or 55 1% of the 109 cases had mild cholecystitis	109 cases
49 or 44 9% of the 109 cases had severe cholecystitis	or 100%
30 or 61 2% of the 49 severe cholecystitics had h d	69 cases
39 or 65 % of the 60 mild cholecystitics had h d	or 100%
22 or 73 3% of the 30 cardiacs with severe chole had well marked heart dis	49 cases
27 or 67 2% of the 39 cardiacs with mild chole. had well marked heart dis	or 71%
5 or 16 6% of the 30 cardiacs with severe chole had decompensation	11 cases
6 or 15 3% of the 39 cardiacs with mild chole had decompensation	or 15 9%
23 or 58 9% of the 39 cases in the 3rd & 4th decades had mild cholecystitis	39 cases
16 or 41 1% of the 39 cases in the 3rd & 4th decades had severe cholecystitis	or 35 7%
11 or 47 8% of the 23 mild cholecystitics in the 3rd and 4th decades had heart disease	17 cases
6 or 37 5% of the 16 severe cholecystitics in the 3rd and 4th decades had heart disease	or 24 6%

tients in the age period between 20 and 40, but found no appreciable difference. In this respect our studies are in agreement with those of Willius and Fitzpatrick<sup>20</sup> who also found that there was no relationship between the degree of pathology in the heart and that in the abdomen.

It should be remembered, however, that the designation "severe cholecystitis" is only relative. It might be severe from the standpoint of pain or other physical discomforts, yet pathologically it may be of minor consequence. It is also well to remember that a mild cholecystitis from the standpoint of the patient or even the physician, may, because of its long duration and insidious character, cause more damage to the heart than the more explosive type of gall bladder

#### MALE PATIENTS

Aside from the fact that cholecystitis in the male is infrequent when compared to the female—16 or 15.5%, there are certain other findings in the male which deserve attention. Analysis

of Table 9 shows that the incidence of cholecystitis increases after the fifth decade—9 or 56% of the cases occur after the age of 50, while in women at the corresponding age, it is only 32%. Heart disease in this group total 12 or 75% as against 61% in the women. Decompensation occurred in 5 or over 41.6% of the heart cases, and 8 of the 12 or 66.6% had severe heart symptoms. The arteriosclerotic type of heart predominated—7 or almost 60%. Obesity was present in 6 or 37.5% as contrasted to 55% in the female group. The severe types of cholecystitis as represented by symptoms, physical and laboratory findings numbered 10 or 62%.

From this table one is tempted to draw the conclusion that when a male is subject to cholecystitis, it is more apt to occur at a later period of life, to be more severe and associated with a marked degree of myocardial involvement.

#### DISCUSSION

Comparing our findings with those of Willius and Fitzpatrick<sup>20</sup> and

TABLE 9  
Data concerning 16 male patients with cholecystitis

Decades	3rd	4th	5th	6th	7th & 8th	Total Number
No. of Pts	2	3	2	4	5	16
Heart Disease	0	1	2	4	5	12
Art. Scl. H. D.			1	3	3	7
Hypertensive						0
Comb. H. & A. S.			1		2	3
Chronic Myoc.		1		1		2
Decompensation			1	2	2	5
Card. Symp.—Severe		1	1	2	4	8
"    "—Mild			1	2	1	4
None	2	2				4
Obesity			1	2	3	6
Diabetes					1	1
Cholecystitis—Mild	1	2	1	1	1	6
"—Severe	1	1	1	3	4	10

Leech<sup>21</sup>, we discover a great discrepancy in the percentage of cardiac affections. Willius and Fitzpatrick report 39%, and Leech 25% of heart disease in their respective series. Our group, as already stated, contains 63.3% of heart cases. In a study of coronary sclerosis with an analysis of 86 necropsies, Willius and Brown<sup>24</sup> found diseased gall bladders associated with coronary sclerosis in 24% of the cases. When one realizes that demonstrable coronary sclerosis is found in but a minority of the diseased hearts of patients affected with cholecystitis, it is not difficult to believe that 25% or 39% are extremely low figures. In a study of 1000 cases of obesity, Preble<sup>25</sup> found 66.2% with cardiac impairment. Master and Oppenheimer<sup>22</sup> in 99 cases of obesity, found that 51% had enlarged hearts and 67% had hypertension. Terry<sup>26</sup> studying 63 patients with obesity found hypertension in 58%. Now, taking into consideration the great number of patients with obesity in the three groups of cholecystitis under consideration, 45% (Willius and Fitzpatrick), 67% (Leech) and 52% (ours) respectively, one may more easily be reconciled with the finding of 63.3% of myocardial disease in our series of 109 cases of cholecystitis.

It is interesting to speculate on the relative effect of obesity or chronic cholecystitis upon the hearts of patients with cholecystitis. Leech<sup>21</sup> and others conclude that obesity is responsible while Willius and Fitzpatrick<sup>20</sup>, Strauss and Hamburger<sup>17</sup>, Mayo<sup>18</sup>, Babcock<sup>16</sup> and others believe that since the patient's myocardium improves after gall bladder surgery, it is proof that the infected gall bladder exercises

a deleterious influence upon the heart.

Our own analysis indicates, we believe, that both factors are responsible. The responsibility of the infected gall bladder is suggested by the evidence of greater preponderance of heart disease in the non-obese cholecystitic cases than in the control group of non-cholecystitic cases. The responsibility of obesity is adduced by the evidence that there is a larger number of heart cases in the obesity group, particularly in the age period between 30 and 50. Another fact helps to throw light on the situation. It is claimed by Cabot<sup>27</sup>, and not without good reason, that most cases of chronic myocardial disease, in which the blood pressure is low, were originally hypertensive, but that as the myocardium broke under strain, it underwent dilatation, with consequent low tension. That hypertension is prominently associated with obesity is a matter of common knowledge and is proven by the studies of Master and Oppenheimer<sup>22</sup>, Terry<sup>26</sup> and others. In our series, although 56.5% of all cardiacs were obese, yet there was hypertension in only 23% of all the cardiacs and in 28.2% of the cardiacs with obesity. Our interpretation is that the infected gall bladder aggravates the already affected myocardium of the obese.

At this point the question may be asked, as to what influence focal infection may exercise on the hearts of cholecystitics. In this series practically every patient had some form of focal infection. The group of non-cholecystitic patients had a similar incidence of focal infection. It is our impression that this finding is the rule in practically every well studied group of

ward patients This study is not competent to draw conclusions in this matter, yet there is no known reason to suppose that focal infection would affect cholecystitis differently than patients with other types of disease

The high percentage of myocardial involvement in the older patients with cholecystitis, particularly in the seventh and eighth decades, is clearly brought out in this study The control group, without cholecystitis, presents a similar condition No doubt, the natural processes incident to old age, may be held accountable for this phenomenon

The small number of male patients in this series, should make one wary of accepting in toto the findings of Table 9, yet we think it is significant In this connection it may be of interest to mention, that of the twelve cases which Babcock<sup>9</sup> reported in 1909 showing the serious effect of cholecystitis upon the circulation, ten were males

#### SUMMARY AND CONCLUSIONS

1 109 patients with chronic cholecystitis were studied

2 63.3% had associated myocardial disease, of which 56.5% were combined with obesity

3 52.2% of the entire group were obese

4 68% of the obese patients had heart disease

5 In the fourth and fifth decades the incidence of heart disease was greater in the obese

6 Hypertension was present in 28.1% of the cardiacs with obesity, and in 16% of the cardiacs without obesity

7 62.3% of the cardiacs were of the chronic myocardial variety, and were not accompanied by arteriosclerosis or hypertension

8 71% of the cardiacs were well marked cases of which 15.9% were decompensated

9 Clinically severe cholecystitis did not differ from clinically mild cholecystitis in its effect upon the heart

10 Males are less frequently subject to cholecystitis than females, and in this series were older, ran a more severe course, and had greater cardiac damages

11 It is adduced, from data obtained in this study, that the infected gall bladder and obesity are equally responsible for the myocardial damage of patients with chronic cholecystitis

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# Cessation of Attacks of Auricular Paroxysmal Tachycardia by the Use of Calcium

## Preliminary Report

By JOSEPH B WOLFFE, *Associate Professor of Cardiology, Temple University*  
and  
SAMUEL BELLET, *Philadelphia*

THE object of this paper is to report a series of five cases of auricular paroxysmal tachycardia, three of which were successfully arrested by the use of calcium intravenously. In all three cases the paroxysms ended suddenly, almost dramatically, the normal rhythm being immediately restored. In two of the three cases, electrocardiograms were taken during the administration of the drug and show the sudden transition.

These facts are of interest because no method of treatment so far known is always uniformly successful in stopping paroxysms. It has been our experience, as indeed that of all who have treated many cases of auricular paroxysmal tachycardia, that in certain subjects the numerous procedures with which we combat the rapid rate remain unavailing at one time or another.

Aside from the extreme mental perturbation, paroxysmal tachycardia carries with it two dangers. First, the patient may die during the attack. Fortunately, this is rare. Lewis<sup>1</sup> who

has had exceptional opportunities for observation in this field, states that no fatal termination has come within his experience unless in the patients who were gravely ill previous to the attacks. Secondly, the attacks may become so frequent that they finally exhaust the heart muscle and lead to death from myocardial failure.

Before referring to the methods we use, it is desirable to review briefly the various measures at our disposal for terminating attacks of paroxysmal tachycardia. They are essentially

- 1 Stimulating of the vagus, either directly or indirectly
- 2 The use of certain drugs

### STIMULATION OF THE VAGUS

This may be obtained by (a) making the patient hold a deep breath, (b) causing him to gag or vomit, (c) ocular compression, and (d) vagal pressure. Whether pressure on the carotid sheath constitutes direct vagus stimulation may be seriously questioned in the light of recent work. Hering<sup>22</sup> has recently presented evidence showing that the slowing produced by so-called vagal pressure is the result of a reflex originating in the

\*From the Department of Medicine, Temple University, and the Mount Sinai Hospital Philadelphia

region of the carotid sinus rather than in direct vagus stimulation and Erben states that compression of the jugular veins stimulates the vagus simply by raising intracranial venous pressure

### THE USE OF CERTAIN DRUGS

Recently, quinidine given intravenously has proved successful in stopping attacks of paroxysmal tachycardia. Singer and Winterberg<sup>2</sup> report a series of nine cases, including one of ventricular tachycardia, thus treated. The doses were 0.4, 0.5, and 0.75 gm. The average dose is 0.5 gm. In six of the cases the paroxysmal attack was brought to an end after an interval varying from a few seconds to ten minutes after the injection. In four of these six cases there was a slowing in the heart rate before the return to the normal mechanism. Boden and Neukirch<sup>3</sup> treated six cases by intravenous injections of quinidine. The attacks ended abruptly in four and slowed in two cases.

Iliescu and Sebastiani<sup>1</sup> report a case with frequent, short paroxysms where quinidine gradually lowered the rate, while it increased the length of the paroxysm until the normal rhythm was resumed. Many observers, Parkinson and Nicholl<sup>4</sup>, Lean<sup>5</sup>, Ottol<sup>7</sup>, Wolfert<sup>8</sup>, Sprague and White<sup>9</sup>, and others have reported excellent results with the use of quinidine by mouth, not only as a preventive of attacks, but as favorably influencing the paroxysms itself. However, failures are not unknown. In the case of Otto and Gold<sup>10</sup> quinidine failed to stop the attacks occurring spontaneously or those induced by epinephrine.

While the great expectations awakened in the beginning by quinidine in paroxysmal tachycardia have not completely materialized, this remedy has proven to be of definite value. Sprague and White<sup>9</sup> conclude that it is effective in about one half the cases of auricular paroxysmal tachycardia in preventing the recurrence of paroxysms.

Other drugs have also been of service occasionally. Digitalis is of value to ward off attacks and may be useful when other measures, including quinidine, have failed. It is important as pointed out by Levine and Blottner<sup>11</sup> that full doses be given—failures being sometimes due to insufficient amounts. De Meyer<sup>12</sup> states that small doses of physostigmine associated with strophanthus are effective in auricular paroxysmal tachycardia, but have no effect in ventricular tachycardia.

Schuster<sup>13</sup> reports a case of simple paroxysmal tachycardia with a pulse rate of 180 per minute, the patient being in extremis as a result of its long duration. As a last resort he gave the patient 1 cc of adrenaline hypodermically. This bringing only very little response, he gave 1 cc of the same intravenously after which the pulse rate dropped to 80. Such slowing, however, was preceded by a period of marked cyanosis during which it appeared that the patient would expire. While the result was prompt, the reaction was unusually marked.

Dukes<sup>14</sup> records a case of paroxysmal tachycardia in which the attacks occurred once or twice a week. He gave parathyroid gland gr 1/10 tid. The effect, he states, was dramatic for the moment and by continuing the tablet medication, the patient

has been free from distressing paroxysms for some years. Corney<sup>15</sup> reports a similar case in which all other methods having failed, parathyroid gland was used, 1/10 gr of dried gland, t.i.d. on an empty stomach and the medication was continued up to the time of report. The paroxysm ceased on the third day and during the subsequent month, only three attacks occurred. Since it has not been definitely proved that parathyroid administered by mouth has any therapeutic effect, the conclusions to be drawn from these two reports are rather questionable.

Aside from the above methods which aim directly at stopping the paroxysm or preventing its recurrence, palliative measures, such as morphine, chloral, bromides and luminal are of value in calming and sedating the patient. It should not be forgotten that when attacks are induced by provocative factors, such as excitement or gastric distention, the latter particularly should be corrected whenever possible.

In our series we gave calcium intravenously in an attempt to stop the paroxysm of tachycardia. This drug has as far as we know not been previously used for this express purpose. The following are the case reports of our patients treated with calcium.

*Case 1* L.P., female, age 50. Patient had no definite cardiac abnormality clinically. She suffered from attacks of paroxysmal tachycardia for several years, of which a chronic cholangitis might have been a causative factor. The attacks usually lasted from one to three days. In 1926, during a paroxysm calcium was administered. Since immediate cessation of the attack was not expected we did not take an electrocardiogram during the period of transition. The normal

heart rate was resumed almost immediately after the injection as shown on electrocardiogram taken 10 minutes later.

*Case 2* M.B., male, age 40. Patient had no cardiac abnormality that could be recognized clinically. He was brought to the hospital in an attack while he was driving a car. He gave a history of similar attacks which lasted from 6 to 12 hours. Calcium was administered. There was no immediate effect. Except for a slight slowing of the cardiac rate, no change was noted afterwards.

*Case 3* B.B., female, age 48. She was diagnosed as rheumatic mitral stenosis with slight cardiac enlargement, but no evidence of decompensation. She gave a history of attacks of paroxysmal tachycardia, lasting from several hours to several days. Two and a half years ago, patient came to the clinic one and one half hours after an attack commenced. Two ampules of calcium were administered and cardiographic records were made. The effect was remarkable, practically instantaneous. The tracing (Fig. 2) shows the changes as they occurred.

*Case 4* R.T., male, age 45. This patient was a case of post-rheumatic mitral valvulitis with slight cardiac enlargement but no decompensation. He had frequent attacks of paroxysmal tachycardia which usually lasted several days. After calcium was administered, he commenced to vomit and perspire. The attack did not cease immediately, but a definite slowing of the cardiac rate was noted and within one half hour, the normal rhythm was resumed.

*Case 5* B.T., female, age 45. Patient was diagnosed as arteriosclerotic heart disease with cardiac enlargement. She suffered from attacks of paroxysmal tachycardia for several years. The attacks usually lasted from one to three days. Calcium was administered intravenously. Sino-auricular block (Fig. 3) was induced and then the normal rhythm was re-established.

In the above series of cases, the patients were given calcium in the form of afeinil or calcium gluconate. The

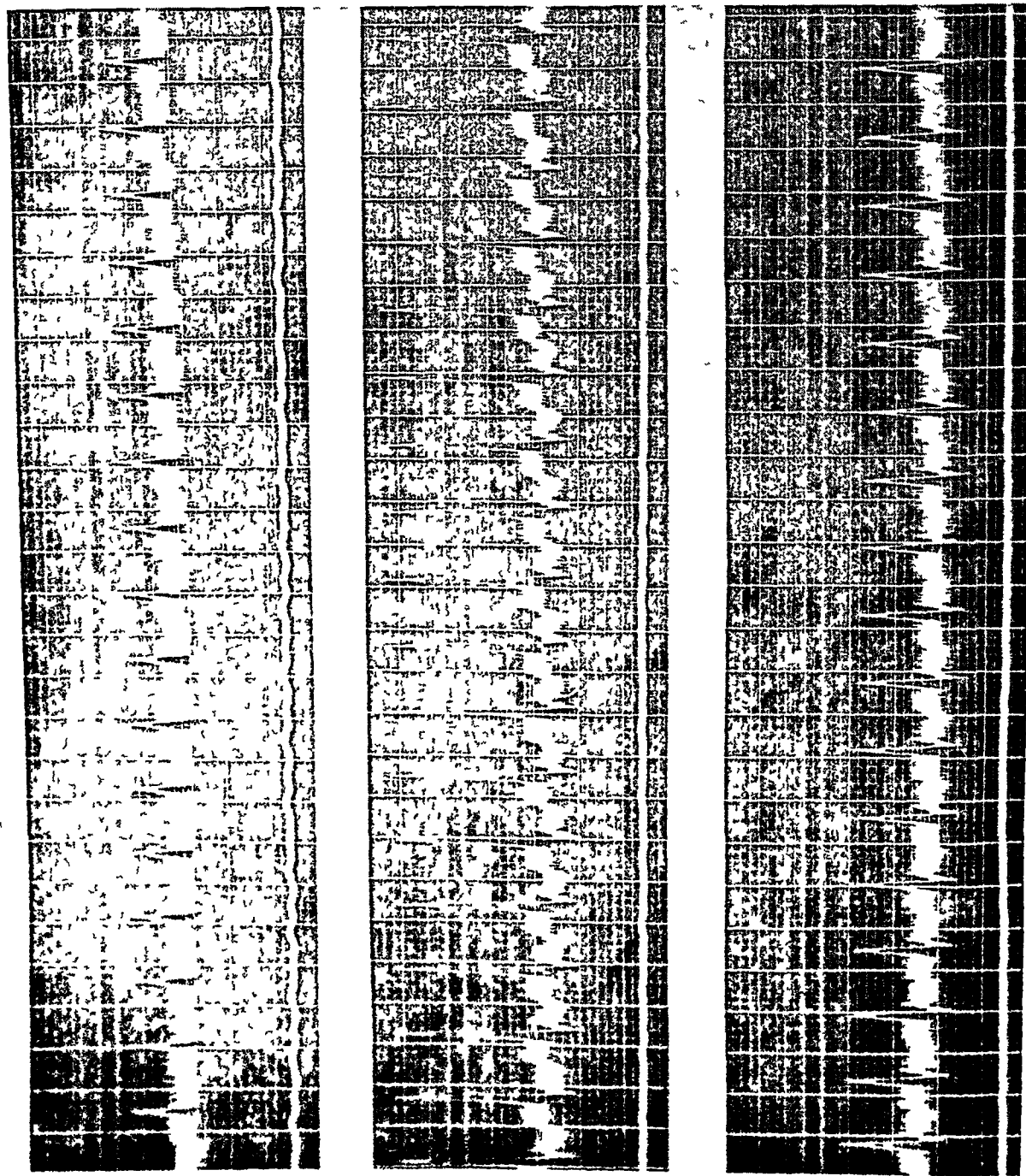


Fig 1a

CASE 1, Fig 1. Tracing A shows an attack of auricular paroxysmal tachycardia, rate 187.5 per minute. An ampoule of afenil was administered intravenously and towards the end of the injection a definite slowing of the pulse rate was noted. The electrodes were immediately attached to the electrocardiograph. Tracing B was then taken probably five to seven minutes after the injection) and shows the return to normal rhythm 68 per minute.

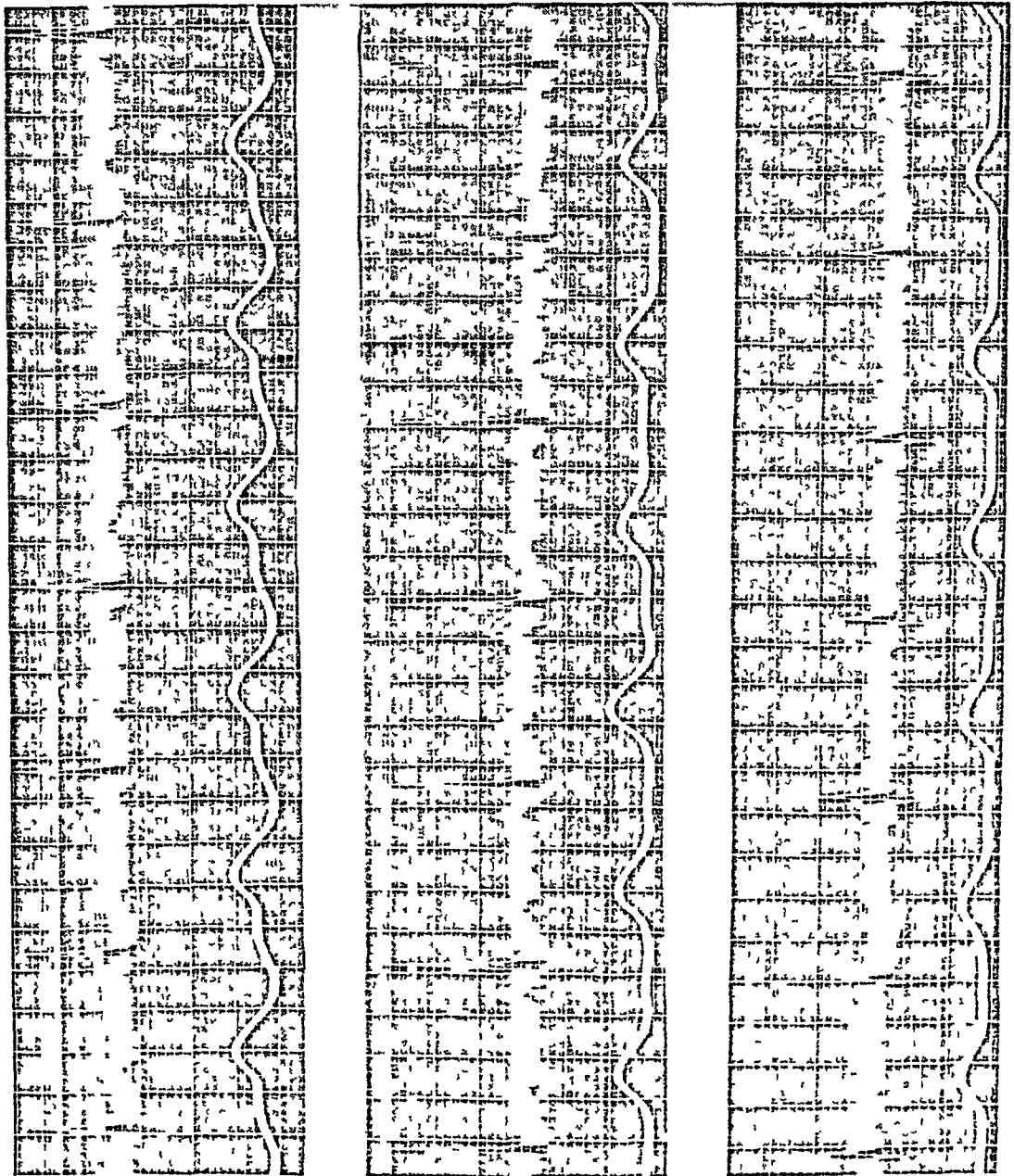
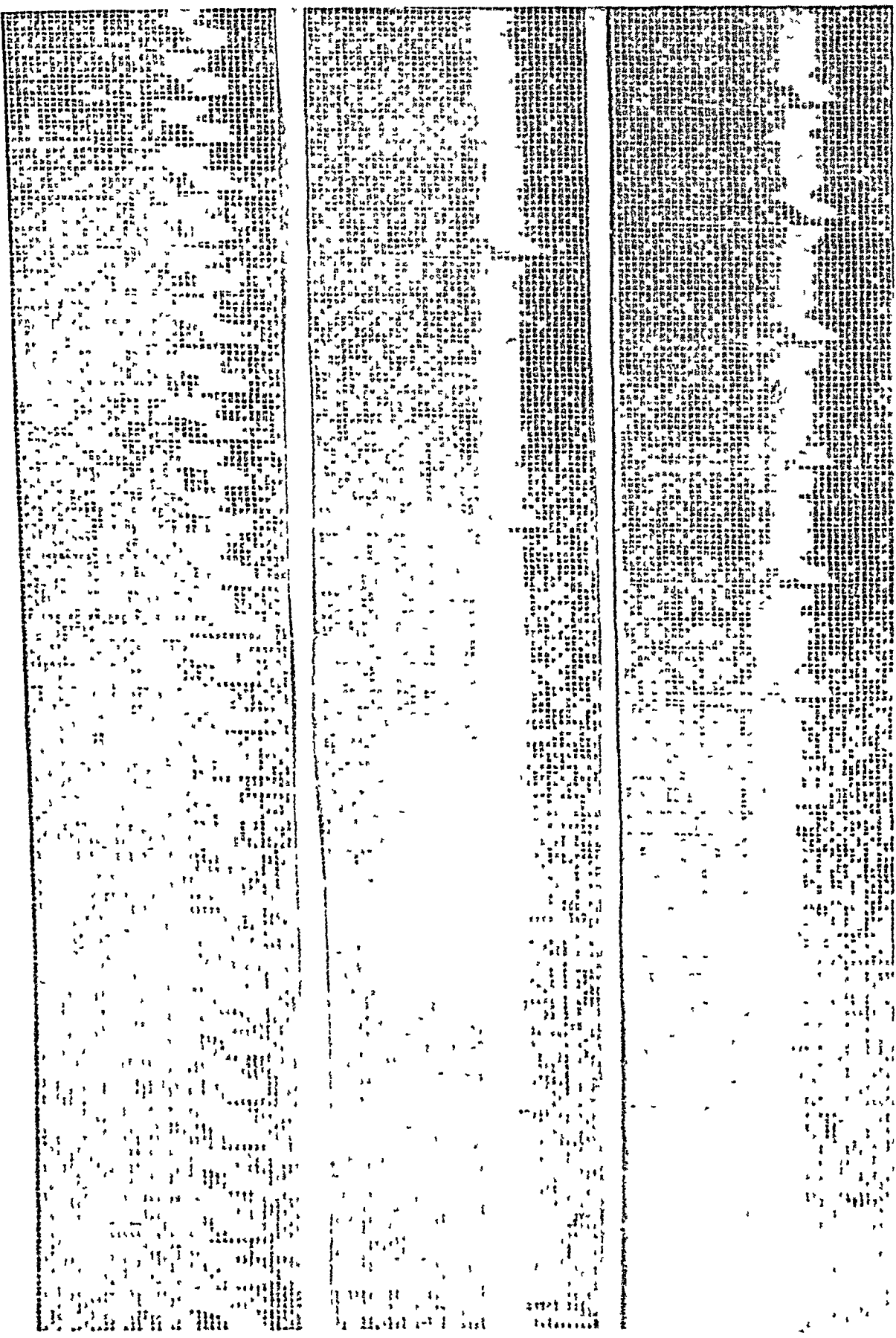
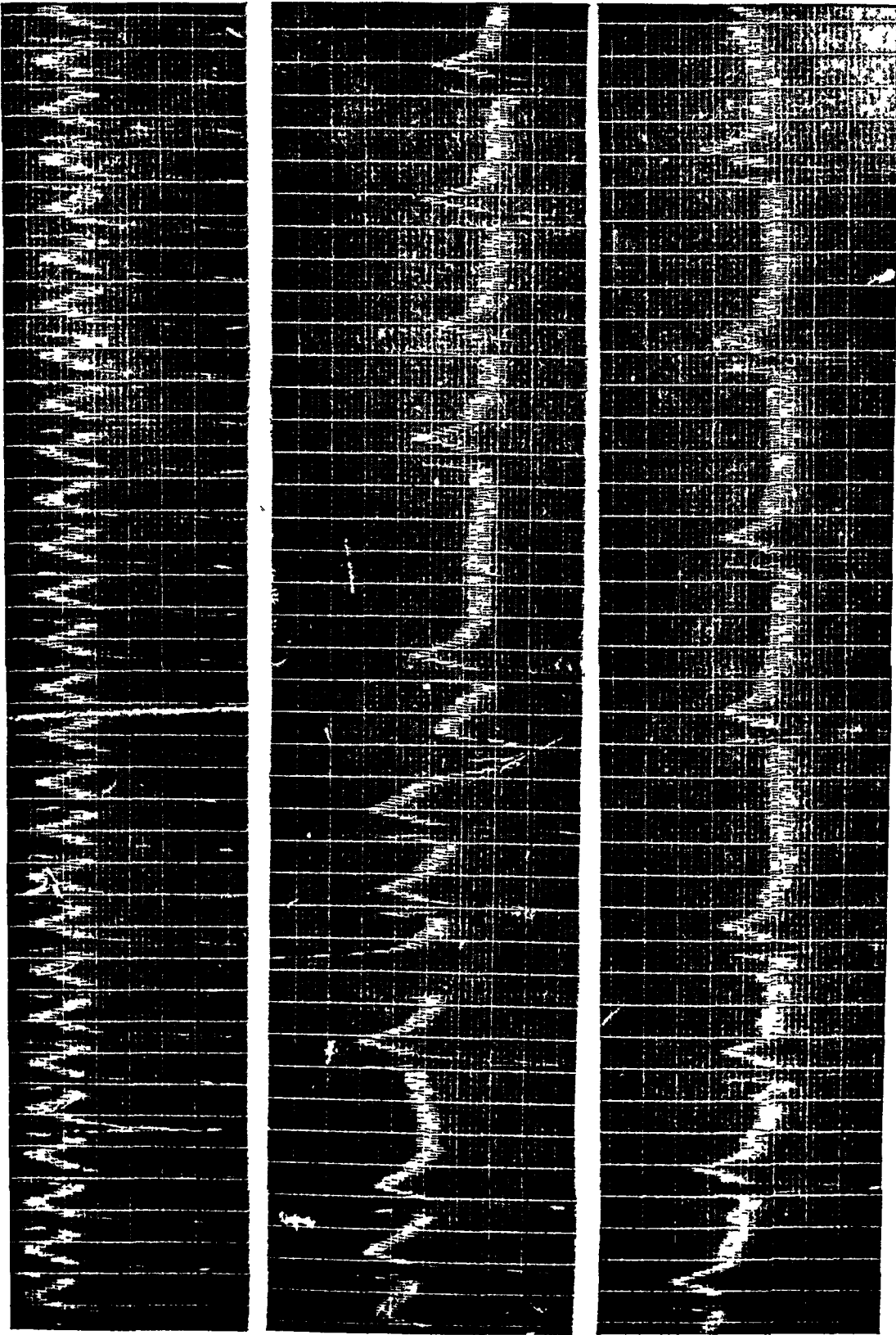


Fig 1b



CASE 3, FIG. 2 A continuous tracing showing paroxysmal tachycardia and the effect of 2 ampoules of afenil. Towards the end of the injection the rate slowed suddenly, a sino-auricular block was developed followed by a premature contraction and the normal rhythm was then resumed. At the beginning of the tracing the rate was 180 per minute and within 15 seconds it was 72 per minute.



CASE 5, FIG 3 A continuous tracing showing a paroxysm of tachycardia, heart rate 200 per minute Towards the end of the injection the rate suddenly slowed and a series of events followed simulating those in Fig 2 The sino-auricular block, however, was of longer duration than in Fig 2 The normal rhythm was resumed in three minutes (Tracing is not very clear, due to restlessness of patient)



remedy must be injected slowly, about five minutes being required to inject 20 c c. During its administration, the patient complains of a sense of intense heat, constriction in the throat, sometimes nausea or burning in the rectum, but all these symptoms are evanescent, passing away in a few minutes. In three cases, the paroxysms ended almost immediately after the calcium was administered and the return to normal rhythm was abrupt as shown by the accompanying electrocardiograms. Cases 1 and 3 received follow-up treatment in the form of calcium lactate, gr XX, t i d. They have been free from attacks since, but whether this is due to the calcium cannot definitely be stated.

In view of the remarkable results obtained, one may pertinently inquire as to the probable mechanism of action of this remedy. Calcium acts on the cardiac muscle by promoting its state of tonic contraction<sup>16</sup>. When present in quantities above normal, or when in relative excess over potassium ions, it causes a condition of tonic contractions which has been designated as calcium rigor. Brule<sup>17</sup>, has shown that large doses of calcium induce in the isolated mammalian heart first an increase in rate, later A V block and finally stoppage in diastole.

Walter and Bowen<sup>18</sup> observed after intravenous injections of calcium in normal dogs an initial increase in the heart rate with no change in blood pressure. Large doses, however, caused extra-systoles, tachycardia and changes in conduction. We have noted these effects in our experiments.

Singer<sup>19</sup> concludes from observations on intravenous administration of

calcium chloride that there is a temporary slowing and strengthening of the heart beat with some decrease in the blood pressure and Lowenberg<sup>20</sup> reports that repeated doses of calcium exert a beneficial effect upon the heart which he terms "cardiotonic".

The mechanism of simple paroxysmal tachycardia is not yet absolutely known. It is supposed to occur as a result of the establishment of an abnormal focus in the auricle. The theory has been advanced recently that it is a form of circus movement.

While the action of calcium on the heart muscle has not been entirely ascertained, it appears generally decided that an over-abundance of calcium ions acts by promoting its state of contraction. Such an action, if at all marked, would work in the direction of increasing the refractory period of the auricular muscle thus tending to inhibit the formation of the ectopic impulse and giving the pace-maker an opportunity to reassert itself. If this is the manner in which calcium, given intravenously acts in stopping a paroxysm of tachycardia, this part of its action at least would be analogous to that of quinidine.

It is interesting to note that whereas in most reported cases where the termination of attacks of paroxysmal tachycardia have been noted, the termination occurs by a post paroxysmal pause, followed by immediate resumption of normal rhythm. In our two cases, after calcium there was a considerable pause in the initial beats following the paroxysm which gradually diminished in the succeeding beats and finally gave way to the normal rhythm.

## CONCLUSIONS

1 An attempt has been made to review briefly the different methods of treating an attack of simple paroxysmal tachycardia

2 A series of three cases of simple tachycardia is reported with electrocardiograms in which the paroxysms were immediately terminated by the use of calcium. It is believed that this is a therapeutic measure which while not successful in every instance, is well worth trying where other methods have failed and where the length of the attack is dangerously prolonged

3 There is some evidence that administration of calcium by mouth between attacks tends to lessen the number of paroxysms

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Since this paper has been sent in for publication, one of us has observed a case of ventricular paroxysmal tachycardia in whom death occurred a few minutes after the intravenous injection of calcium chloride (10 cc of a 10% solution). This case was not treated under our direction. The patient was 68 years of age with an advanced grade of arteriosclerotic heart disease and was almost in extremis. The drug used was calcium chloride which has a greater toxicity than either afeinil or calcium gluconate, it was given rapidly through a large bore needle instead of slowly and the patient had been previously heavily digitalized. These may all have been factors in the final result. Calcium is given intravenously for many conditions and fatalities are extremely rare. However, we deemed it advisable to note this occurrence in our paper, which is the only one which has come to our attention.

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# The Diagnosis of Gastric Lesions by Intra-Gastric Photography

## Preliminary Report\*

By REUBEN FINKELSTEIN, M D , F A C P , *Brooklyn, New York*

THE X-ray examination of the stomach with the barium meal reveals merely a shadow picture of the barium mixture as limited by the gastric walls and borders. Hence, when a defect in the upper or lower border occurs it is filled by this fluid mixture and thus its shadow is outlined. Again, this fluid mass also lends itself to distortion by peristalsis or any irregularity in the stomach wall caused either by an organic disease or a simple spasm of the wall.

From the pioneer work of Hemmeter, Rieder, Holzknacht and others it was soon discovered that lesions on the anterior and posterior walls of the stomach are by this method recognized with difficulty and often not at all. This is because the opaque mixture fills the entire stomach, thus obscuring any defect that may be present in its walls. Many attempts have been made to diagnose such lesions by variations in the technique during the X-ray examination. By manual compression of the abdomen during fluoroscopy or by giving small amount of the barium mix-

ture and watching the course of the rugae, filling defects may sometimes be noted in the anterior or posterior walls. Ulcers have often been found by these methods. Many more have been missed, especially when they were shallow or situated in unfavorable positions among the thickened and at times hypertrophied rugae at the pylorus.

For many years gastroscopy has been used in an attempt to visualize the lesions of the interior of the stomach. But the natural limits of the field of available vision and the unwillingness of many patients to submit to the difficult procedure involved, has prevented the full use of the gastroscope. Consequently, there has long been a feeling among gastro-enterologists that some method should be devised to picture the interior of the stomach on a photographic film, by means of a camera inserted through the esophagus into the stomach. Naturally, such a camera would have to be no wider than an ordinary stomach tube and be in some way connected with a proper source of light of adequate intensity so that photographs could be taken. Such an instrument has actually been devised by Mr. Bach working under the

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\*From the Gastro-Intestinal Service of the Medical Department of the Brooklyn and P.S. New York Hospital, Dr. Raymond Clark, Chief.

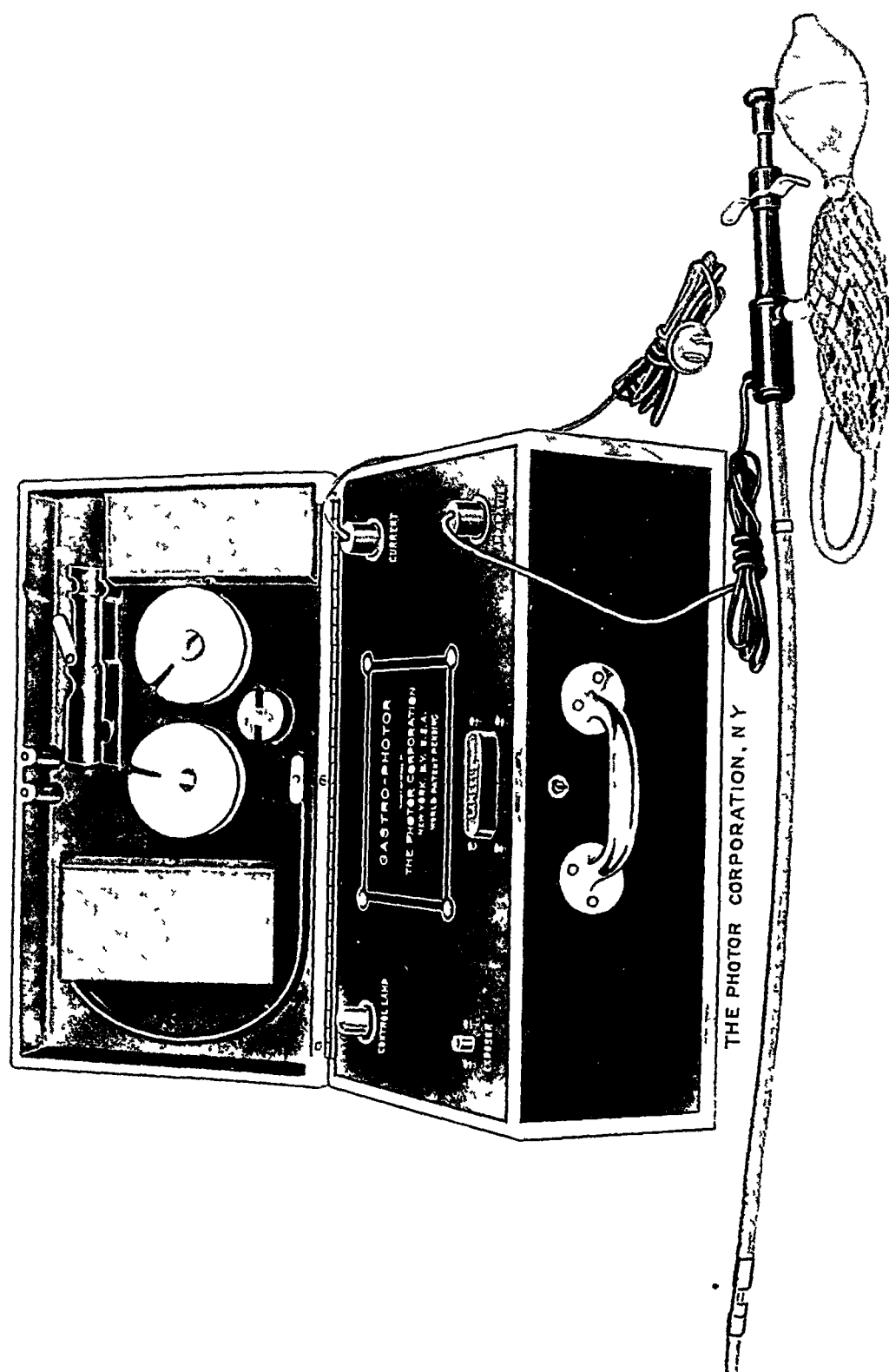


FIG 1 Gastro-Photograph with camera

direction of Professor Porges and Dr Heilpern at the Wenckebach clinic in Vienna

This instrument, Fig 1, consists essentially of a semiflexible tube carrying at its distal end a double camera, an upper and lower, between which is a small electric bulb so constructed that when activated by a transformer it yields a bluish white light of 12,000 candle power for  $1/120$  of a second and is then destroyed. The transformer takes its energy direct from the house lighting current. Each camera contains four small films regularly disposed in a circle, and by means of two pinpoint holes, an upper and a lower, a stereoscopic picture is taken by each film of a 90 degree arc of the circumference. Thus at one exposure eight double stereoscopic views are taken. These eight films are so marked that when developed one can readily tell which part of the circumference of the stomach is pictured on the film.

These pictures are of course, best taken on the fasting stomach which

should be further evacuated from its overnight secretion. This is accomplished by introducing a double stomach tube and placing the patient on the left side in the trendelenberg position. Through this tube the stomach is first filled with air, then one side of the stomach tube is released and through the other side air is continually pumped so as to keep the stomach from collapsing. The tube is then withdrawn slowly and in this manner the stomach is completely emptied. In cases of overnight food residue the stomach is first thoroughly washed out and then emptied as outlined above.

The patient is then placed before a fluoroscope, the gastro-photor camera is introduced and its position localized. The stomach is then inflated with air through a special opening in the tube. The shutter is opened, the transformer button pressed, the shutter closed and the camera is withdrawn. The whole procedure from the moment of introduction of the camera to the time of its withdrawal should not be more than

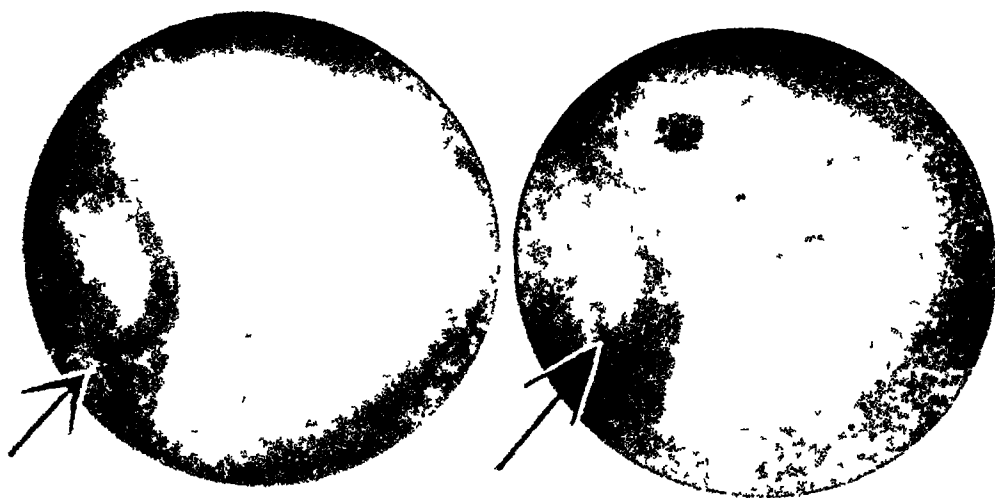


Fig. 2. Stomach taken out of the pylorus proven in operation.



FIG 2A X-ray of carcinoma shown in Fig 2

$\frac{1}{2}$  to 1 minute. The films are then removed from the camera in a dark room, developed and enlarged to about ten times their original size. These pictures should be studied in detail. Proper skill is easily acquired after comparing a number of these pictures with surgical and autopsy material wherever available.

This report is limited to the first twenty-five cases in which we carried out this procedure. In the beginning we had a few unsatisfactory results but as our technique improved our pictures were uniformly good.

Four of our series were operated upon. In three of these cases the diagnosis was made on the roentgenological findings and confirmed by the gastro-photor pictures. Figs 2, 2A, 3, 3A, 4. In the fourth case, No 38082, the roentgenological films were negative. The fluoroscopic examination showed a suspicion of pathology at the pylorus. The gastro-photor pictures showed definitely the presence of two ulcers at the pyloric region. Though the opera-

tion in this case was performed by an experienced surgeon, he was unable after opening the stomach to feel the ulcers with his finger reaching to the pylorus. Upon autopsy, however, the gastro-photor diagnosis was confirmed and the two ulcers found, Figs 5, 5A, 5B.

Of the twenty-one cases not operated upon, two gave evidence of prepyloric ulcer on the X-ray films. In these two cases the gastro-photor pictures showed only the presence of spasm of the gastric wall, Fig 6.

*Case No 37470* Diagnosed as gastric ulcer, was confirmed by fluoroscopic examination which showed an incisura with a niche on the posterior wall near the lesser curvature. The gastro-photor pictures did not show the ulcer but gave evidence of hypertrophied rugae among which a small ulcer could easily be hidden so that it could not be visualized on the picture, Fig 7.

*Case No 37345* On X-ray showed a limited mobility of the pars pylorica but no definite defect was observed. The gastro-photor pictures revealed an ulcer near the pylorus, Fig 8.

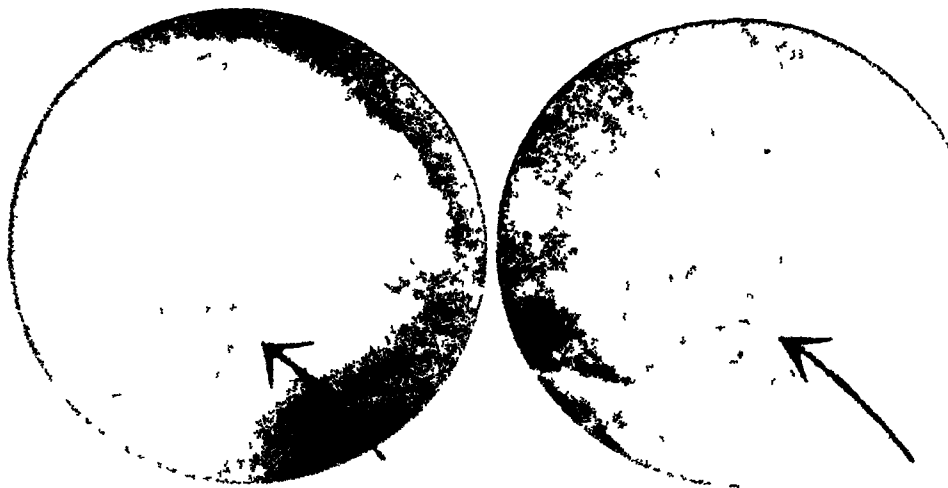


FIG 3. Carcinoma involving the lesser curvature and pylorus. Proven at operation.

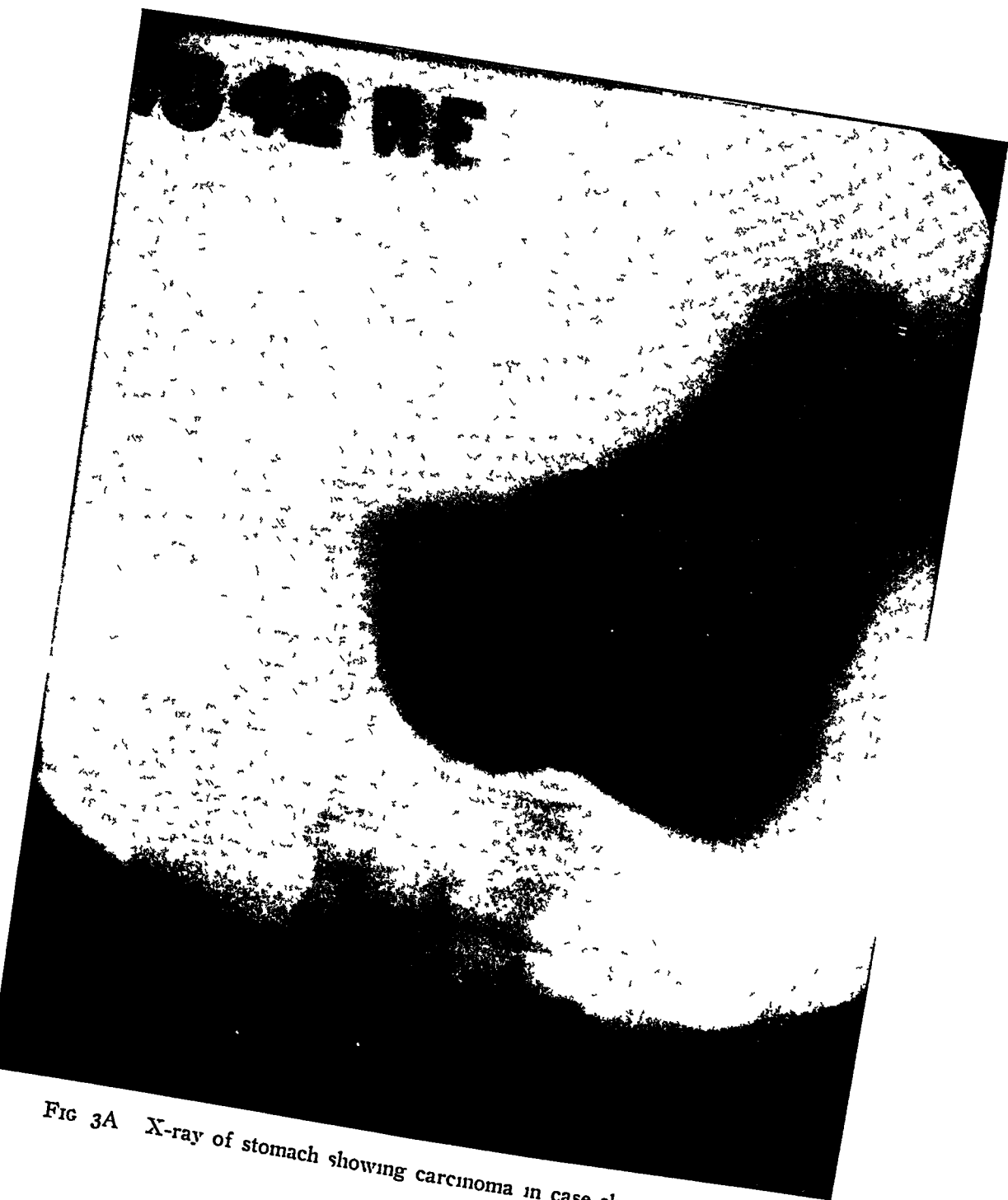


FIG 3A X-ray of stomach showing carcinoma in case shown in Fig 3



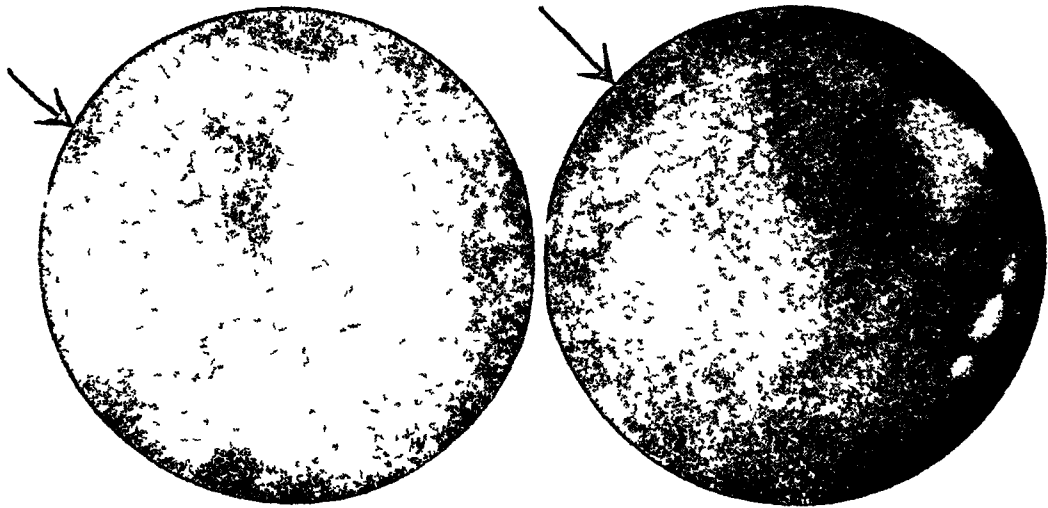


FIG 4 Case No 36764 showing ulcer on lesser curvature near the cardia, proven at operat on

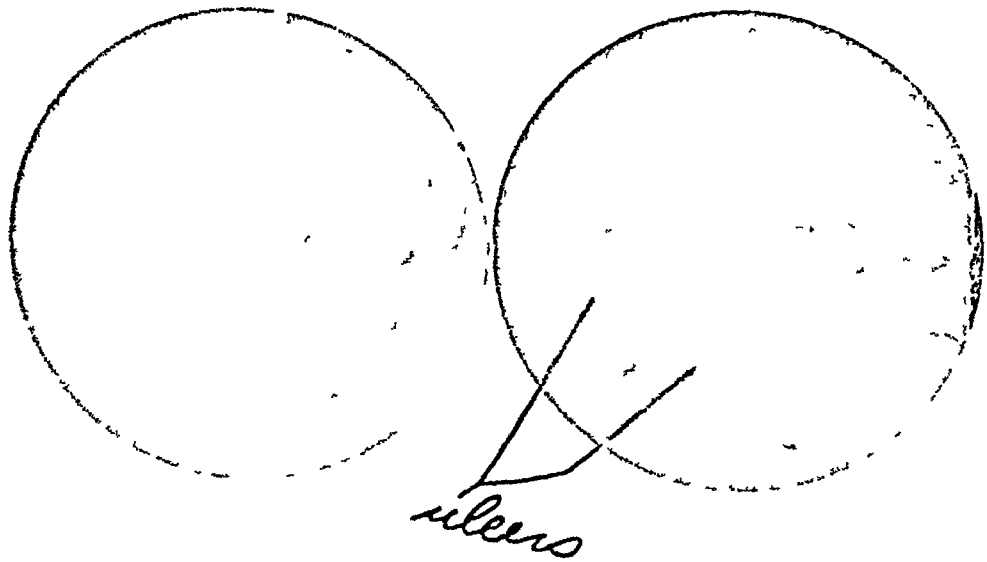


FIG 5 Case No 38082 showing two ulcers on the lesser curvature not found on X-ray but at operation and confirmed at post mortem

*Clinic Case No 501* Where patient complained of gastric disturbances with definite history of sour eructations, epigastric pain coming on from one hour to one and one half hours after meals and relieved by food and soda and often by vomiting. Occasionally the patient noticed blood in the vomitus. The X-ray films showed the prepyloric region and the duodenum in spasm. Nevertheless, under the fluoroscope the duodenum was well outlined and appeared to be normal, but the prepyloric region appeared to be defective and was quite tender to palpation. Here again, the gastro-photor pictures showed the presence of an ulcer on the lesser curvature near the pylorus probably in the process of healing, Figs 9, 9A

The remaining cases were all negative for ulcer both on X-ray examination and the gastro-photor pictures. Four of these showed hypertrophied mucosa on the gastro-photor pictures, Fig 10. The final clinical diagnosis was chronic gastritis in one and chronic cholecystitis in the others. Among the remaining cases we diagnosed one as lead colic, another as a retro-peritoneal lympho-sarcoma. The latter was con-

firmed by operation. The final interesting case was one of achylia of unknown origin. It is interesting to note that in these last three cases the gastro-photor pictures did not reveal any pathological changes in the gastric mucosa.

The number of cases reported is not large enough to give a complete demonstration of the value of the gastro-photor but enough evidence has been given to insure for it a place in the diagnostic armamentarium of the physician. Like all other means of diagnosis it is not infallible, and will not replace the X-ray or clinical evidence of gastric disease. There are, however, a large number of cases where the diagnosis cannot be made and only a gastro-photor picture will reveal the lesion.

My sincere thanks are due to Dr Isidore A. Feder and Dr George Ashe for their valuable assistance in this work.

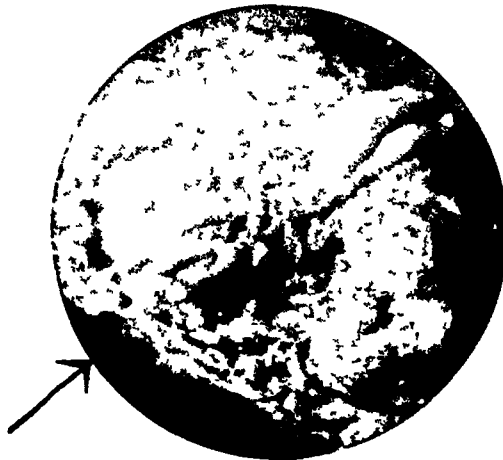


FIG 5A Case No 38082, picture of pathological specimen showing ulcers in picture in Fig 5

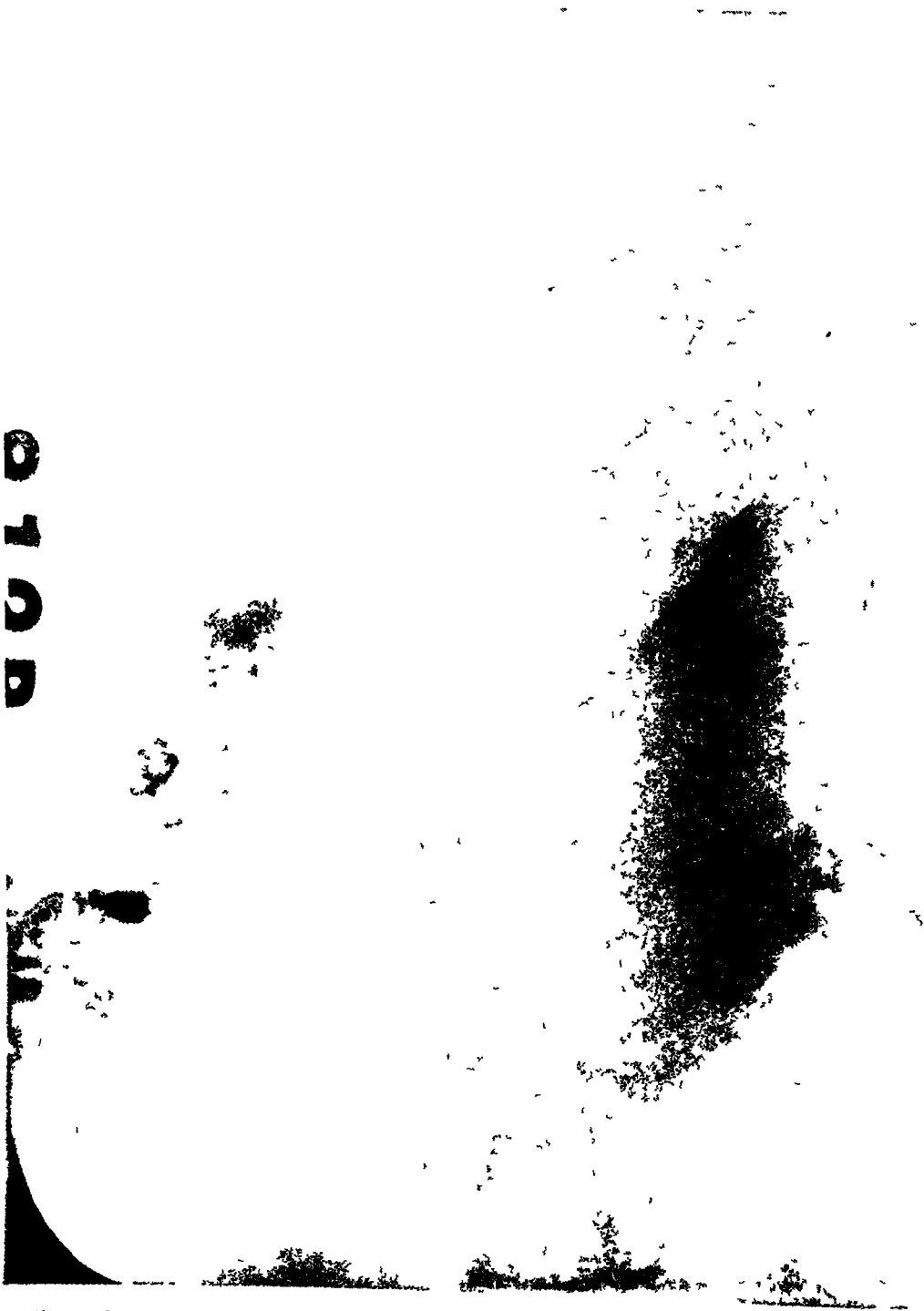


Fig 5B Case No 3692, X-ray of stomach showing no ulcers but which were found on post-mortem

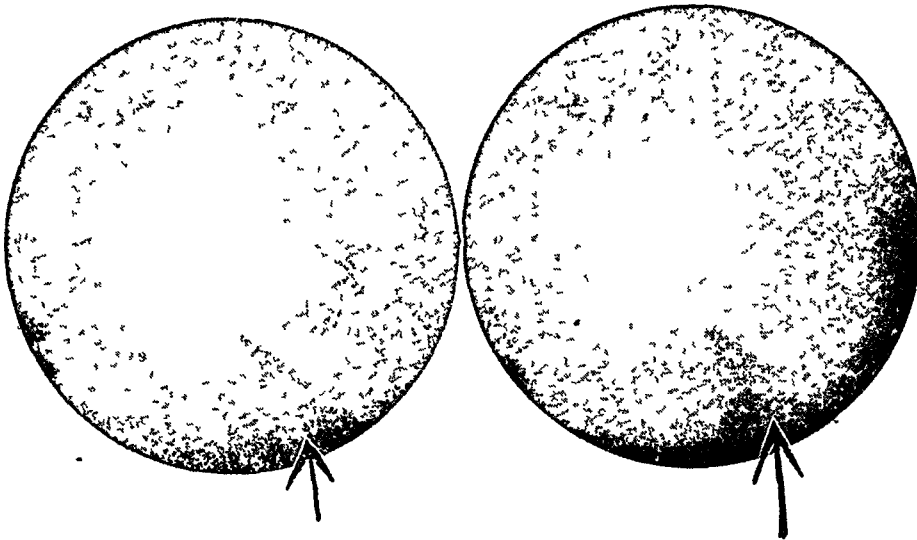


FIG 6 Only spasm shown in case where X-ray shows a prepyloric ulcer

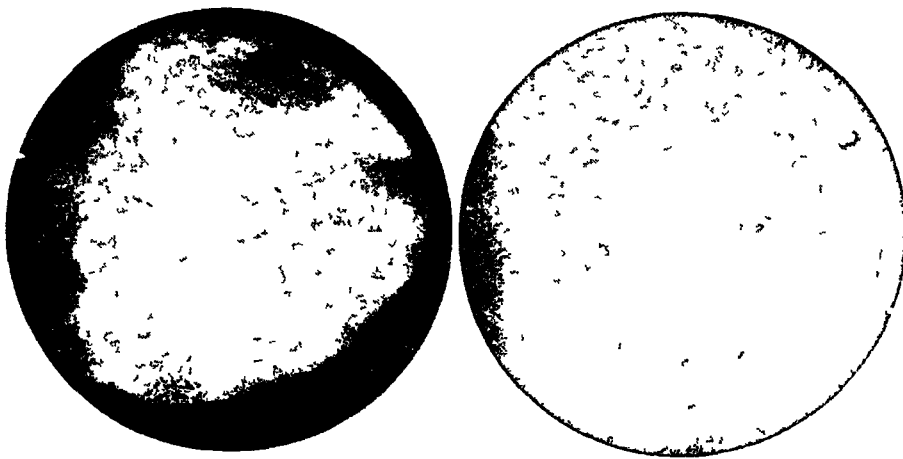


FIG 7 X-ray diagnosis is gastric ulcer Picture shows only hypertrophied rugae among which a small ulcer can easily be hidden

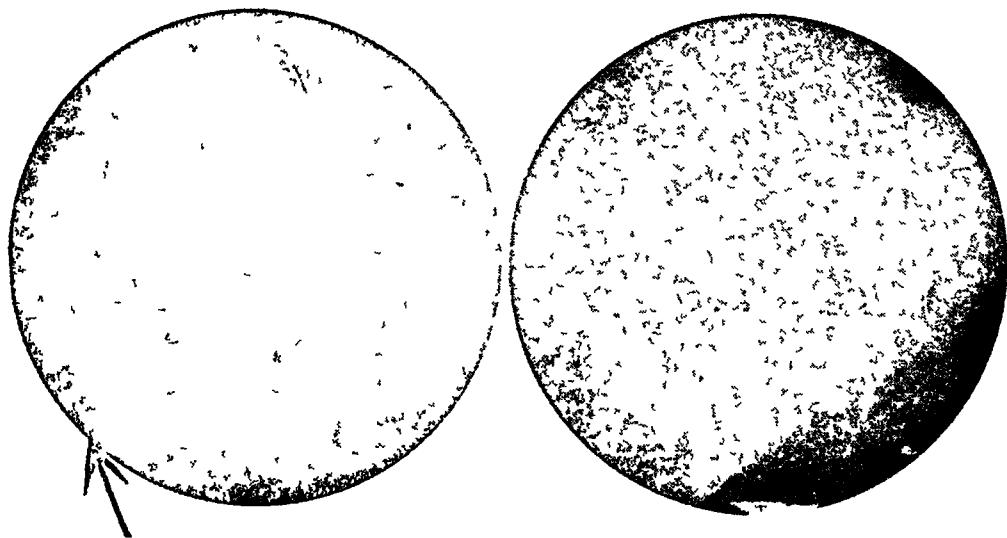


FIG 8 At fluoroscopy there is some evidence of pathology at the pylorus Picture shows an ulcer in this region

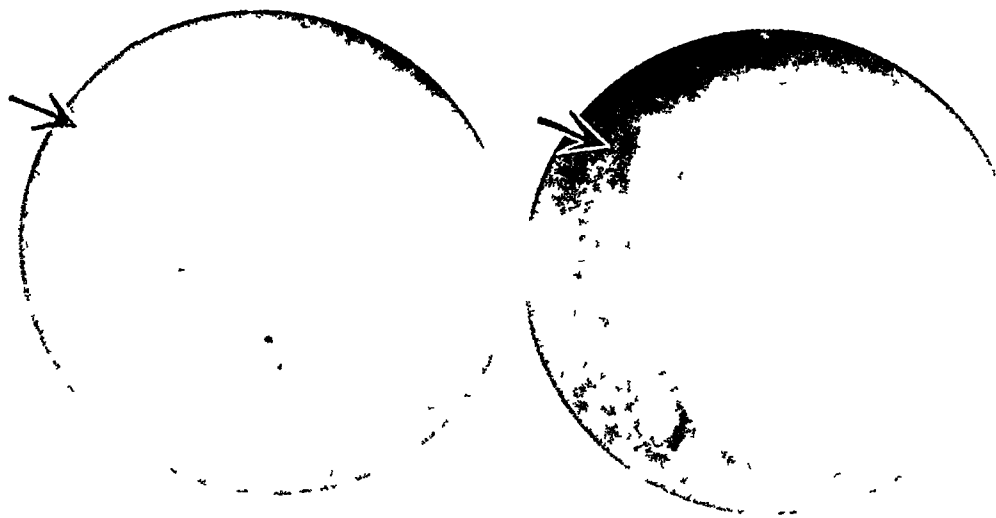


FIG 9 The X-ray pictures are indefinite, the fluoroscopic examination shows a distortion in the prepyloric region. The Gastro photor pictures show an ulcer near the pylorus or the lesser curvature



FIG 9A X-ray of stomach showing spasm of prepyloric region Gastro-photor picture  
Fig 9 showed ulcer in this region

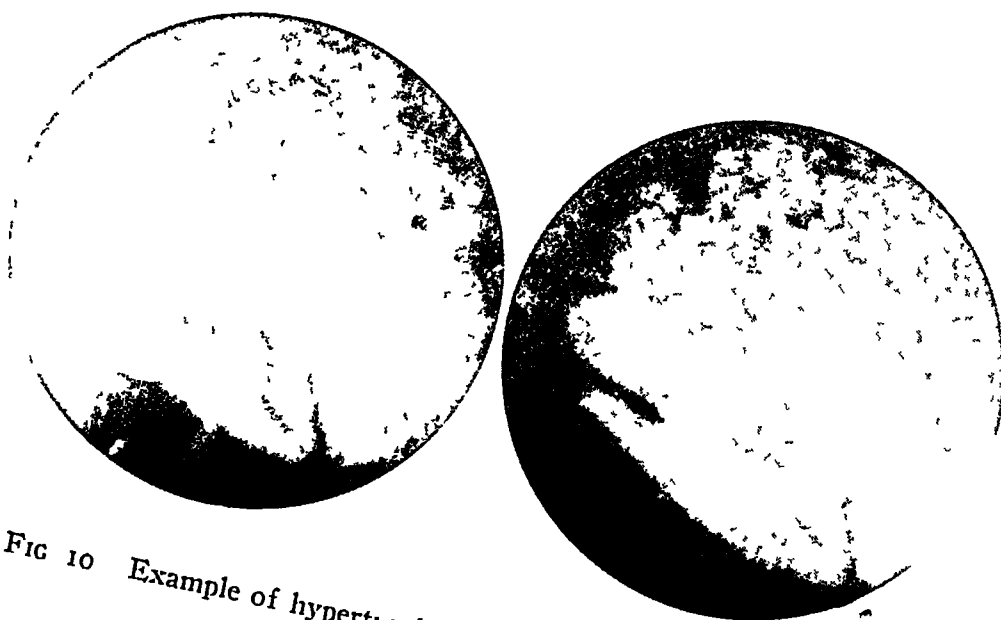


FIG 10 Example of hypertrophied mucosa in case of cholecystitis

# Hereditary Juvenile Pellagra\*

## A Resume of the Literature

By CHARLES JAMES BLOOM, M D , B Sc , F A C P , *New Orleans*

### INTRODUCTION

PELLAGRA has at this writing vital problems, the nature of which still remains unsolved. In the last decade, exhaustive and intensive research, clinical, anatomic-pathologic, and experimental studies have added scientific interest to a disease known to Europe since 1735. It has, in a brief space of time, diffused itself throughout the greater part of the Old World and, as years passed on, was noted and described in many other countries.

The cause of the disease, the frequency with which it affects the infantile age, and the treatment, are topics most considered by the present day medical world. For a long time, one believed that it was a disease exclusively of the adult, forced to fatiguing field labor, exposed to the summer heat of the sun, nourished with scanty and improper food, when the more excessive the fatigue, the greater was the consumption of his forces. In order to find observations of pellagra in infancy and childhood,

it is necessary to go back to the works of the old writers, which have remained untranslated. One of our present day writers has well said "If some of the early literature was modernized in language and expression and published in a journal of today, it would prove capital and stimulating reading to the most up-to-date student of the disease. Many of these early articles are characterized by a depth of comprehension, a wealth of assimilative experience, an accuracy of observation, an orderliness of arrangement, a well balanced judgment, and a breadth of scientific spirits which might be emulated by the modern medical man."

In the main, there is no attempt on my part to give to the profession original viewpoints other than that described in my first paper\*, or to take sides at this time regarding the etiology of pellagra. Personal references will be indicated and in the last paper of this series, a résumé of my findings will be discussed at length. These papers are the results of seven years of study. The translations were taken from many languages, especially from Italian, French, Spanish, Russian and German sources. There has been a rearrangement of thoughts, altered

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\*This series of articles on Pellagra in Infants and Children was made possible through the munificent gift of Mr and Mrs Russell Clark, of New Orleans, in memory of their daughter, Alma Villere Clark.



translations and omission of all references not pertinent to infants and children. The writer's interest is predicated by the fact that the thorough knowledge of the cause of pellagra, of its peculiar manifestations in the young, is wanting in our literature. By the presentation of these papers, I trust that further study and experimentations will be stimulated, that a better understanding of the infantile type will necessitate an earlier diagnosis. Further than this—a completed bibliography is given to the profession. In conclusion, remember that the child is the father of man, that our efforts should be expended in limiting the mortality of children. If my efforts to present facts will aid the child in the slightest way, my compensation will then be complete.

### *Hereditry*

Still limited to some countries, not well known in its multiform clinical aspects, perhaps also less numerous and profound those somatic and psychic alterations which characterize the heredo—pellagrin, and demonstrate degeneration consequent on the slow and progressive toxic process, while the strangest and most diverse hypotheses regarding its etiology reigned, is it not strange or unusual that the infantile form was accepted with but slight consideration or denied entirely?

With the multiplication of the observation, of the works on the subjects; with the perfecting of the means of investigations, and of our knowledge of the general pathogenesis of diseases, and in particular of pellagra, it has not been difficult to discover that the disease is hereditary in the nature

under manifold aspects, even if not with the same frequency as in the adult, and clinical forms, well characterized and distinct, have been studied. But specially there has been ascertained with clinical and experimental investigations, the injurious blastophthoric effect which the pellagra of the parents transmits to the product of conception, on a par with alcoholism, with syphilis, with malaria, and with other toxic and infective agents.

Pellagra is one of those diseases whose etiology is not yet perfectly known. Hence, the study of its epidemiology assumes an extraordinary importance, since it is known how from the exact knowledge of the epidemiologic phenomena one can many times, at least exclude with certainty some groups of etiologic factors. It is not necessary to call to mind of how many diseases it has been possible to affirm the infective nature on the basis of the demonstration of certain epidemiologic characters. Inversely, the lack of specific phenomena, in the study of the epidemiology, can be a sufficient criterion to negative special etiologic hypotheses.

In the recording of those authorities who accept on the one hand, and reject on the other the question of hereditary pellagra, one is impressed by the numerous Italian references. Unquestionably, the physicians and scientists of Italy, through generations, have had a better opportunity to observe this disease in all of its forms than any other country of Europe.

The classic signs and symptoms, other than those mentioned casually, or described in the translations of

*Gemma*, will be reviewed in detail in another contribution

Infants who develop pellagra; children developing stigmata of degeneration in a short interim of time after birth; those who succumb to marasmus, malnutrition and inanition where these entities can be traced to pellagra, and lastly, individuals born of pellagrous parents, who perhaps do not develop infantile pellagra, but in later life exhibit classical symptoms of pellagra, will all be discussed in due time

The transmission of pellagra by heredity was suspected a long time ago by *Odoardi* (1776) and by *Albera* (1781-1806). This belief was held also by *Strambio* (1786-1794), who could establish that up to that time the largest part of the pellagrins are born of pellagrins, that the offspring of these even in youngest age are more easily seized by the disease, that in the various families it is with difficulty that one finds an isolated case of pellagra, but several blood-relations (consanguine) are attacked together

"As to age, I have already published many histories of pellagrous children, not only under 12 years of age, but 6, 4, 2 or even sucklings." He also mentions that among 126 pellagrins he found 15 individuals at the age of 1 to 25 years, wherefrom of course one can draw no conclusions specially as to child-age

Strambio speaks of a man born from a pellagrous mother, who in his turn has had a daughter pellagrous even from infancy, and this one a baby boy with a nasty cutaneous affection. But his contemporaries have seemed little inclined to admit an influence of

pellagra on the descendants and in these the hereditary predisposition

Later *Fantonetti* (1830) narrated that he had "seen a baby boy at the age of one year, who by the desquamation of the neck and of the hands even to the middle of the forearm one would have had foundation for calling him pellagrous. He was born of pellagrous parents, and had been carried around and also held in the sun; hence it is not in any way contrary to reason that in some cases it can happen that from pellagrous parents may issue a child with organic conditions which may bring it also to suffer from pellagra." And farther on he has added "It seems very well that pellagrous parents can give origin to children, who will easily fall into pellagra, particularly as they may remain in the same conditions of food, of shelter, of work as the parents

Concerning the influence of inheritance *Roussel* (1842) speaks in manner worthy of the highest consideration. He distinguishes three sorts of hereditary factors. The *first* sort includes those diseases which originate in the parents and find continuation in the infantile organism: those are the *morbi communiti* of the ancients, the *morbi parentales*, as syphilis or variola. The latter disease, undergone by the fetus, gives to this and to the following child immunity. In this sense pellagra may not be hereditary

The *second* sort included diseases, whose germs are instilled during the development of the forthcoming being. These germs are at first not manifest, the child seems healthy, and only with the development of the child did they come to maturity and lead to devasta-

tion. As example he alleges the inheritance of scrofula, of cancer, and of other cachexias. Of course, to our present day view these examples no longer correspond. *Roussel* does not reckon pellagra among this sort of congenital diseases.

Under the *third* sort he understands now the simple similarity of the infantile organism to the parental, which lets the growing one seem less "resistant" against like detriments. Here he reckons pellagra, and in this sense he grants an inheritance in case of this disease, but not the inheritance of this disease. Today we would say, in case of pellagra heredity is the "predisposing" cause (constitutional or predispositional inheritance). But then such "hereditary" pellagra may not have a special clinical form.

*Ghiotti and Longhi* (1844) conclude, in their investigations, that of the 1,319 persons examined, who were descendants of 184 pellagrous families, 671 were healthy, and 648 were pellagrous. Their study deduces two very interesting conclusions: (a) a tendency for the affection to be more commonly transmitted by parents to children of their own sex and (b) that the malady is more often inherited from the mother than from the father.

*Calderini* (1846), in a recapitulation of 96 couples where both parents were pellagrous, noted that there were 116 sons and 106 daughters pellagrous; in 160 couples where the father was pellagrous and the mother was healthy there were 64 sons and 49 daughters. In another series of 175 couples, where the mother was pella-

grous and the father was healthy, 30 sons and 38 daughters, born of this union, had developed the disease. In addition, he offered some very interesting data regarding hereditary pellagra. In the 1,005 patients admitted to the City Hospital of Milan, 1844-46, 300 of this number developed the disease before the end of the third year—one-fifth of this number was male, and one-fourth female. Later on he refers to 352 pellagra cases, of which 83 were under 3 years and 15 between 3 and 12 years. Indeed the tenderest infancy may even be the selected age.

The Piedmont Commission in 1847 closed its report affirming that for the most part one is born pellagrous, exaggerating thus the truth of the clinical postulate.

*Lussana and Frua* (1856) state that "the pellagra of infants appertains to individual children of pellagrous parents," and note again that in the children "the pellagra is mild because in the first stage."

*Gemma* (1871) as the most noted and criticized exponent of hereditary pellagra has said:

"This is a fact quite painful for the man of natural science, this being obliged to go again so many times over the same road, finding on the way the obliterated footprints of his predecessors. In this manner at every step arises an obstacle to progress, and the near horizon of truth removes itself by degrees as we advance in our studies. And this fact is so much more painful, because it happens more often not by the discovery of scientific materials new and contradictory, but because the man makes himself slave

of his theory and humiliates the expression of the facts to his own idea. This has happened also in admitting hereditary pellagra."

"*Roussel* had already at his disposition an archive of histories, and the confession of distinguished pellagrolologists; he possessed the fruits of his scientific travels in Italy and Spain, he could place in combination the statistics of *Lussana* and *Frua*, demonstrating that the etiologic element of one-third of the pellagrins of the great Hospital of Milano was heredity, the statistics of *C Gallo* and of *Calderini* demonstrating that the disease had begun under 3 years, in 300 individuals. Instead he terminates with saying, 'qu'il n'est pas vrai qu'on naisse pellagreu; qu'il n'est pas vrai qu'un germe pellagreu se transmette par l'heredite'.

"How he has arrived at this conclusion, through a series of contradictions, it is useless to recall. After having admitted in one page that 'l'heredite est un fait aussi unanimement reconnu,' in the following page he writes 'Lors qu'on a etudie de tres-pres les familles pellagruses, on est amene a ne pas faire consister le fait de l'heredite dans la reproduction de la pellagre proprement dite, et tout entire chez descendants des pellagreu.'

"It is convenient to say that he has been fully convinced that the fact of heredity was an insuperable barrier, was the wall of China against which must of necessity beat to pieces the arms of the defenders of the maldic poisoning, if one set himself to fight it with effort, and with a power of talent worthy of better cause."

"And in what manner could he combat a fact unanimously recognized? To feign to be ignorant of the facts for a pellagra encyclopedist, such as is *Roussel*, was impossible. To deny them would have been indecorous boldness. Then? Then it was convenient to deny them, facts the most explicit, the most fearful; those which could be attacked in one way or in another to confess them, giving to them a different interpretation. In short to stay on horseback, to form a neutral ground, on which one could be comfortable at his own beautiful ease. This he has done in fact, and one cannot deny that he has done it with much self-possession and courage, if not dexterity.

"Therefore one inherits pellagra, no one today contests the reality of it, but it is a metaphor, but it is not properly pellagra and all entire pellagra; that is, one inherits and one does not inherit, because that which seems pellagra is not pellagra, although the pellagrolologists may call it pellagra; in short I do not know how to express myself, but *Roussel* has understood all.

"He commences with denying that some cases were pellagra. In the history of pellagra he asks, has one imagined facts of an appearance analogous (to the parental diseases), I speak of those unlucky newborn ones or sucklings, who have offered all the symptoms of confirmed pellagra? The cases of *Zecchinelli* specially, it would seem that they ought to be related to case of pemphigus of the newborn (disease which would itself be frequently a syphilitic disease). As for *Strambio* (note well *Strambio*), who

has said that the greatest part of pellagrins owe their disease to pellagrous parents, he believes it opportune to correct him by substituting for greatest part (*la maggior parte*), beaucoup

"He reports the beautiful description of *Sacchi* (reference and date not found) on the hereditary influence, description which I wish to reproduce today."

"It happens to me sometimes to observe little creatures with all the indications of a perverted vegetation. I cast a glance at their parents, and withdraw my looks shuddering. This little being will remain vitiated for all the course of its life, which will not be long, or if he shall seem to develop himself a moment, that will be to plunge down again later under the influence of the causes, which will alter more and more his organization already altered. It is a common custom in our country districts,—speaking of a person who suffers of ills long and unknown, in the most beautiful years of youth and of virility,—to say that he has inherited his ills; and the ills are no other thing than pellagra. There is then a particular or pellagrous habit; a good long time before the development of the pellagra, one can recognize the individual who will be attacked, by his vacillating and uncertain step, by his eyes with a yellowish reflex, by his fixed stare, by the color of his face pallid or yellowish, by the tarsi of his reddish eyelids, by his cracked lips, by his scanty hair . . . by his forehead furrowed with wrinkles beyond his age, by his soft musculature, in short by his suffering and apathetic aspect."

"Well then! To the energetic picture which manifests the observing mind of our Italian, and which today merits several additions, what does *Roussel* respond? . . . Whether there are exaggerated features in this picture .

"But to the detailed observations of *Lussana* which demonstrated heredity to *Lussana*, how does he respond? They are adults who have lived in the pellagrogenic conditions, that is, have eaten infested polenta and who for that reason have become pellagrins

"And it goes very well. I have heard that a bizarre brain takes it into his head to demonstrate with historical and philosophical arguments, that Napoleon I has never existed. As for me today I shall believe in him. But then what is science? A stage, and we are the actors who await the applauses and the hisses of the cultured public, according as we represent well or badly our part.

"In the same manner that *Roussel* and companions deny the heredity in the strict sense of pellagra, I would be able to deny the heredity of rachitis, of scrofula, of arthritis, of cancer, and even of syphilis

"But *Roussel* himself cannot deny that there exists something hereditary. Well then; this something is the pellagrous substratum (*fondo pellagroso*). 'Il n'est pas vrai qu'il (*Sacchi*) peint une realité, à laquelle il a fallu un nom particulier et pour laquelle on a créé l'expression encore si mal définie de fond pellagreu' Behold then the grand discovery. The children of pellagrins are—as he says—of a sad aspect, cacochemic, of lean tint, of downcast air, but nothing more, these are not pellagrins, but they have the

pellagrous substratum, and become pellagrins when they have been subjected to the use of polenta. Hence there does not exist the weak fomite, the pellagrous germ of *Lussana*, the substratum exists. For pellagra one cannot use the expression *heredity*, which represents a true cognition, which signifies a fact which we see all the days, and one as ancient as reproduction itself, which if not yet explained, remains and will remain always an acquisition of science, one must use a new expression, created for the purpose, and so defined badly.

"No, with the means of the terms, with the subterfuges, with the substitution of words the sciences are not created, not in such manner are erected edifices which can resist the impact of the centuries, one erects on the sand and the first breath of wind will scatter the fruit of our labors.

"*Roussel*—was he then competent to judge of such a question? See the answer by himself 'la pellagre a chez nous un champ plus limité qu'en Italie, elle y est moins grave, et les influences de l'hérédité y sont moins manifestes'. He then who judges *Strambio* and *Lussana* is a man who lives in countries where the pellagra has less heredity influence.

"We are not ignorant of the travels of *Roussel* in Italy, and specially in Brescia, a province extraordinarily infested by such disease. But is it possible to see all the phases of a disease of the people so protean, or of a constitutional stain, seeing it for a few days? Who will be more competent, the one who judges it in such manner, or the one who has lived long years

among the destructions of pellagra, observing the vicissitudes of it?

"And here is necessary a justification. I have taken aim at *Roussel* for his ideas on pellagrous heredity, because, as one may say, he understands all the reasons which seem to oppose themselves to this fact. I never combat the man, but the idea. For that matter, I have the greatest respect for *Roussel*, as scientist and pellagrologist. If he, dominated by a preconceived idea, which without the outfit of sufficient proofs, presented itself to him as fascinating, because according to him it must of necessity form the basis of the etiology, of the pathology, of the prophylaxis, and therapy of pellagra, if he, I say, fell into some error, what wonder? I appreciate very much his work, I have studied it profoundly, it is certainly a monument of glory for its author, if it were only as a well ordered pellagrologic encyclopedia.

"After *Roussel* has come the work of *Lombroso*. He has admitted, with brief description, pellagra with imperfect development and mild hereditary pellagra. But the opposers would be able to reply that the first is not pellagra, but an organic alteration which can develop in the children of all the deteriorated organisms, the second is not hereditary, but dependent on equal dietetic conditions. On all one can cavil.

"In what manner to render demonstrated as fact which is already universally admitted? With statistics? The opposers would not have lent faith, were there not statistics already? With clinical observations? It is always the best means, but it was suitable to use it with the greatest pre-

cision; since if there had been found a single pretext, such and such a subterfuge, they would have responded the usual ritornelle of the common hygienic conditions, or else of the mistaken diagnosis. The maidists all pretend to a particular prerogative, that is, not to be able to diagnose and know any pellagra but theirs. They are like the priests of all the religions, who declare impious all those who do not think as they do, and devoutly they curse among themselves. What pleasing minds! . . .

"Up to the present time this subject has been rather deflowered than studied; one has established as a fact, that is, that even infants (*bambini*) can be subject to pellagra, and that in them it depends on heredity in the maternal line, but that solely in etiologic scope, without seeking to eviscerate this important point of the pellagrolologic pathology.

"Let it not be believed that here I wish to occupy myself with the etiology of pellagra in general. I ought to establish as a fact merely that the chief cause of the pellagra of infants is *heredity*, a thing—to tell the truth—observed by others

"For the rest the imprint of heredity extends itself still farther, and while the parents, who suffer from neuro-muscular pellagra, but are in sufficient state of health and of constitution still quite good, usually give children well developed, those who suffer from atrophic pellagra, give children also in this condition.

"The process of dentition does not seem to have in pellagrous children a greater influence than that which it has in other infants, children of

healthiest parents. In all the cases observed by us, and diagnosed as pellagra of infants there was no work of inchoate dentition (*dentizione incoato*—that is, begun but not finished). On the contrary, the gravest case and the one which has terminated with death, was, at the age of *2 years*, provided for some months with all his teeth, which had developed themselves without any inconvenience, while the pellagric phenomena have manifested themselves in him with the beginning of the summer.

"A singular fact, and which certainly will be evident to the attention of our readers is this: *that one inherits the special pellagrous form* To *Lusana* is due the merit of having introduced the most practical division of the pellagric forms. The present studies on heredity, while they come to confirm such division, demonstrate this new fact in our game, that one can inherit the form. It goes without saying that this fact ought not to be accepted in the sense of a mathematical precision. In the sciences of observation and specially in pathology, it is difficult that that should happen. Thus, for example, if a father has had cerebral pellagra, and the son also has had such, in this last one could be associated some intestinal phenomena, but the cerebral phenomena, however, will be the most salient. That which constitutes the fact under discussion is this, that the parents affected by cerebral pellagra give almost always cerebral pellagras in their children. The same goes said for the dermo-intestinal, for the neuro-muscular, and others. This fact is certainly an important acquisition, because it demon-

strates that not only is such a disease hereditary, (ereditario) like all the other hereditary (gentilizi) diseases, but is more manifestly hereditary than scrofula and than tuberculosis

"And now, how can one say that pellagra is not inherited all complete? Perhaps because in many individuals it manifests itself when they have reached a certain age? First of all, who is there who can assure us that those individuals have not manifested the pellagrous phenomena in their first youth? In order to exclude this supposition, it would be necessary that a physician should have observed them for a long series of years, that which cannot be done, except by one who has practiced medicine for 30 or 40 years in one same locality. But even admitted that the individual, first was healthy and had all at once in adult age manifested the pellagrous phenomena, what can one infer from it? Even tuberculosis, to which no one denies heredity, develops itself in the greatest number of cases in youth and in adult age, rachitis on the contrary develops itself in infants and in children, scrofula and syphilis in infants, children and adults; cancer in late virility. Pellagra, developing itself hereditary in every age, would resemble scrofula and syphilis

"That the hereditary pellagra cannot be explained with the co-existence of the same hygienic and domestic conditions, let us believe results sufficiently illuminated, not only from the pellagra of the newborn, but also by the accompanying case histories. We have seen that this manifests itself, not only in the peasants, but in the well-to-do of the country, in the poor suburbanites,

and even in the rich citizens, when the germ exists in the family. The hygienic conditions, however good, are not sufficient to exorcise entirely pellagra, when it exists in one's own genealogy. And the number of well-to-do of the country who suffer the disease is quite other than small, I could bring forward a quite larger quantity of cases, if I had not determined some limits for myself.

"And now we make a comparison between this heredity so certain, so evident, which so much resembles that of scrofula, with the heredities of mercurialism; 'and in general,' writes *Lombroso* (*Sull'etiologia della pellagra riposta ad alcune obbiezioni*) 'the female workers in mercury bear children scrofulous, rachitic, tabetic, and affected by grave cutaneous diseases.' And this, to speak truly, is quite a strange manner of understanding pathologic heredity. I shall be able to demonstrate, and I will demonstrate it in what follows with the facts, that from pellagrins can be born children, scrofulous, rachitic, tabetic, oligocythemmic, but with that I will never say that those scrofulous ones, nor those rachitic or tabetic ones have inherited pellagra. I will say only that the children have inherited pellagra, when they shall be pellagrous as the parents have been. It is natural that unhealthy fathers give unhealthy children, but this fact is not sufficient to constitute pathologic heredity. I see in general, that old parents give life to delicate children; does one then inherit old age? These examples go absolutely refuted as hereditary diseases, when one does not wish to affirm that scrofula and rachitis are the same



thing as mercurialism. But there are cases more explicit. 'Mayr (loc. cit) has noted three babies of workers, who on the 14th day from the birth, presented the mercurial tremor; on one (male) it has presented itself the very day of parturition, in a girl after a year with stomatitis and ptyalism. Another girl born while the mother—very rich and well nourished—was a prey to mercurialism, has presented smallness in the person, salivation, lack of teeth; the other children born after the mother was cured of mercurialism, were very healthy.' Behold another history taken from *Russmaul*. 'Laborer, who 12 years previous has had to suffer by effect of his profession, mercurial salivation, loss of teeth, was married three times the four children of the first wife, who was a worker in mercury, all sickly have died, three of consumption, one of gangrene of the feet, and so also the two children of the second wife. Of the third wife, the children born while she was working in mercury, have died; the others placed in the world after the mother ceased from the work, have survived.'

"These facts I believe have no need of criticism, these, if one believes thus, may also be called hereditary, but it is certain that then it is fitting to trace a great line of demarcation among the pathologic heredities. These cases near to the birth, can be considered as a continuation of the paternal poison, or maternal, and to be counted among the diseases which are called congenital, rather than hereditary. The single case farther from the birth is a girl of one year. She has had stomatitis and ptyalism, which

could originate in other causes. But we are not accustomed to contest the diagnoses of the adversaries. It is necessary that we establish the enormous diversities which pass between this and pellagrous heredity. The adversaries of heredity, supporters of poisoning, reproached us, years back, that there were no cases of pellagra, well assured, near to the birth. We have presented them, and we have presented also some of them quite distant from birth; now in our turn we can say present to us cases of poisoning distance from the birth, which have the characteristics of hereditariness.

"Likewise a mother affected by smallpox can bring forth a child with smallpox, but no one will wish to compare this fact to scrofulous heredity. A mother infected with syphilis can bring forth a syphilitic; but what difference, if instead the mother, being healthy and having suffered formerly of syphilis, brings forth a child in whom later is developed syphilitic lues? The first case would be congenital, or contagious; the second hereditary.

"In the sense generally adopted (I take the definition from *Roussel*) one understands by heredity, not the disease itself of the parents transmitted to the infant in all its development, but a principle, or if one wishes, a germ detached from the parents, whose development does not take place except with the development of the organism.

"It is in such manner that is hereditary—scrofula, rachitis, cancer, the tuberculosis; and in such manner is hereditary also pellagra. A child of tuberculous persons can attain in health, for example, to 20 years, and

in that age become tuberculous. Before that age, the most advanced ascultator will find sometimes a perverted constitution, but nothing which can make him pronounce the diagnosis of tuberculosis. A child of cancerous persons can become cancerous at 40 years, but before that epoch the wisest clinician would not find the signs of the disease. Later, perhaps, the progress of the microscope and of animal chemistry, will explain to us these unknown things, but until that day it is fitting that the medical practitioners respect the facts, if they do not wish to walk in chaos.

"The same is repeated in the comparison which one wished to make between the heredity of alcoholism and that of pellagra. The hereditary ones of alcoholism of *Burdet* are thin, cacochemic, poor in spirit, often idiots, subject to scrofula and above all to convulsions and to the cerebral maladies (*De l'ivrognerie et de ses effets*). The cases of *Gunsam* are insane; the 16 cases of *Marce*, son of an alcoholic, have all died before 3 years of cerebral accidents, except an epileptic. And these are all hereditary alcoholists, hereditary like the tuberculous, like cancer? What ought one to reply? That the spirit of partisanship blinds, even to delirium, also the men the most profound in science. Well then, from now on, if a son of a tobacco smoker shall suffer of pneumonitis, we shall say that that is hereditary pneumonitis by reason of nicotinism.

"Yes, also from pellagrins can be originated children sad, unhealthy, cacochemic; also in the children of pellagrins there is a frightful mortality, also in our histories every one can

observe this fatal hecatomb of young lives. But these cases are not pellagrous heredity. These must rather form part of an interesting study, which would be that of the transformation of the hereditary diseases. *Roussel* has said that 'the families in which exists the pellagrous substratum are extinguished and disappear easily under the blows of different occasional causes, with which pellagra has nothing to do'. We also have spoken of these facts, and we will bring others subsequently, but let us not fear that these may weaken pellagrous heredity.

"We ought then to conclude that the manner with which one inherits pellagra is quite different from that with which are inherited the known poisonings. And also here, as in other facts, the pellagrologic clinic and pathology stand against the theory of the poisoning. Besides, if the heredity of this disease presents itself under five forms, it would be fitting with such theory to admit that the poison of the maize had five manners of acting, or that in this cereal existed five poisons, each of which was partial to an organic system, dwelling in this even to the third generation.

"And now what is the mild hereditary pellagra of *Lombroso*? It is a hereditary neuro-muscular pellagra. Whoever then considers that not always—it is true—does one die of this form, but that still it torments sometimes the entire existence of an unhappy one, that the onset or rhythm having developed itself, this lasts sometimes several months, that it is necessary often to use all the known reconstituents, to use energetic reparatory therapy on the nervous system;

and that with all that the patient is not profited—sometimes—except with the return of the autumnal season, this one will not know how to understand in what such 'mildness' consists

"After these proofs and those adopted in the pellagra of sucklings and of newborn, we ought to conclude that pellagra is a *hereditary disease*. With that it is quite natural that one does not deny the acquired or primitive pellagra. The two facts not only can, but they must necessarily both exist; because to become hereditary, it is requisite that a disease introduce itself in some individual of the family. In other words, pellagra goes frankly compared to all the hereditary (genitizzî, family) diseases.

"We have victoriously repelled all the objections which have been made on the subject. One has said that the pellagrous infants did not exist, and I have demonstrated that pellagra is developed in sucklings; one has said that that of infants was not pellagra, but cacochemic delicateness, and I have found infants with erythema. One has said that many pellagras of the authors could be interpreted differently, and I have presented some of them so detailed and circumstantiated as not to be able to leave any doubt; one has said that the appearance of heredity depended on the influence of the same pellagrogenic cause; but I have demonstrated that, even changing the hygienic conditions of a family, one can develop pellagra when it exists in the same

"But in order to demonstrate, that the pellagrous heredity is a heredity, like that of other hereditary (genitizzî) diseases, and not a substratum

of depauperization, on which the pellagrogenic cause determines the pellagra, we have in hand organic proofs which certainly have escaped *Roussel*. These proofs result from the constitution itself of the pellagrins. We desist here from speaking of the pellagra of imperfect development, which too clearly presents its characteristics; also the common hereditary pellagra can be quite well known objectively."

*Bassi* (1880) apparently had not specialized in the particular disease he now discusses, but states, nevertheless, that "while it is generally declared that pellagra is not contagious, one wishes nevertheless to call it hereditary. That does not seem to me as yet legally proved.

"In order to assure ourselves of it, to doubt it no more, it would be suitable to take some babies (*bambini*), and repeatedly, in order better to assure one's self of the truth, some babies just born of pellagrous parents, and brought soon into families in which individuals do not nourish themselves at all with maize, or if they feed themselves with this, they use it in the healthy manner referred to above by me; and here nursed by nurses who will feed, or feed themselves in the same manner, and kept here in the midst of the same families up to the adult age, living and exercising themselves in the manner of the persons composing the families themselves, which (the families) in order better to ascertain the truth—it would be well that some should be dedicated to field labors and others to various factory labors; and it stands then to see whether there manifests itself in one

or the other age in these children of pellagrins the pellagra which afflicted their parents; and, manifesting itself in this case alone, one will be able to say legally that pellagra is hereditary"

*Lombroso* (1885), speaking of pellagrous heredity, divides it into two species, the one very grave, the other mild. From what he writes, it is easy to convince one's self that his exact observations are directed to mark the characteristics which distinguish the hereditary pellagra from the acquired in the adults, rather than to study the pellagra of infants. In other words, he establishes that which one would call the *habitus* of the pellagra. In regard to the gravest hereditary pellagra, he writes that "it manifests itself from the second year of life, rarely with desquamation, more often with pains in the epigastrium, pyrosis, voracity, uncertain walking, easy fear, diarrhea, yellowish aspect as in the fevers of malaria, and retardation in the development"

*Sepelli* and *Lui* (1899) explained their interpretation of heredity as a "transmitted degenerative condition in which, as may be the case with alcoholism and certain chronic intoxications, there occurs essential modifications in metabolism and in the functioning power of the nervous system, determining in the descendants of pellagrins a weak constitution, and producing a state of lowered resistance, which leaves the individual especially susceptible to the maize toxins

"Well then, in 173 insane pellagrins we encountered pellagrous heredity, now direct (95 times), now indirect (6 times), or that is, in the enormous

proportion of 58.3 per cent. Further, we encountered pellagrous heredity not rarely in forms plainly degenerative, such as phrenasthenia and epilepsy. Taking then into examination in our patients of mind those morphologic anomalies which have a value more or less accentuatedly degenerative, we made note how the insane pellagrins offered us a considerable percentage of degenerative signs, principally in such respects as the cranial malformations and those of the face, the pathologic expressions of goitre and of rachitis"

Their findings have been substantiated by *Bonservisi* (1899), in his accurate statistics of the Mantovan pellagrins, established that, out of 2,718 children of pellagrins, 1,093 were dead under 5 years, about 160 in the following (years), and the others living presented degenerative marks, gastro-intestinal disturbances, or true forms of pellagra. Of the 1,460 living, 59 had habitual intestinal disturbances, 81 were true pellagrins, and 311 weak and sickly. Hence, while in healthy families there was under 5 years, 290 per mille of mortality, in the families of pellagrins it was 402 per mille, almost double.

"*Antonini* (1902) has found in man a confirmation of the experimental pellagrous teratogenesis of *Cem*. Examining the degenerative characteristics of 59 hereditary pellagrins, he found them 38 times, that is in 62 per cent, while in 98 pellagrins *not hereditary*, he established them as a fact only in 18, or that is in 17.9 per cent, which demonstrates how children of pellagrins become subjected to ar-

rests of development and to deviations with a frequency by far greater than those who originate in families immune from pellagra.

*“Conclusions.* There exists a pellagrous heredity confirmed also by experimental researches demonstrating how the nutrition with spoiled maize diminishes the procreative power and favors the development of teratological products.

“It is interesting to examine the composition of the single families divided by communities. Hence, I set forth the tables which are the result of the spoils of the tabulations returned by the sanitary officers with the indications. For brevity I limit to the first hundred of families, certain that no modification of the conclusions will be able to be brought by the pursuing of the inquiry, because these first hundred families belong to communities of all the commissions without any selection.

“We have, therefore, that one hundred *non-pellagrous* families have given 616 sons, of whom 200 have died, and 416 are living at the moment of the inquiry.

“Hence the proportion between the sons dead and the living is that of 48.07 per cent.

“There have been born dead seven, and aborted nineteen

“In the 100 pellagrous families, on the other hand, there have been 523 sons, of whom 225 have died and only 298 were living at the moment of the inquiry.

“The proportion, therefore, between the sons dead and the living is that of 75.5 per cent.

“There have been fifteen born dead and thirty-two abortions. Thus it remains confirmed from this numerous statistics that pellagra diminished also in man the generative potentiality, and that in the sons of pellagrins there is a mortality of a good third above that which is verified in the families of normal persons in the respective communities, and precisely in a proportion of 100 to 159. That is, if in a certain number of normal families 100 sons die, in the same number of pellagrous families 159 of them die”

#### *Influence of the Blood of Pellagrins on the Product of Conception*

The subject was the object of experimental researches by Professor Ceni (1905) himself, of the Istituto Psichiatrico of Reggio Emilia, who first of all has established that the blood of pellagrins in general, and in especial manner of those affected by actue forms, was constantly presenting physio-pathologic modifications, in direct relationship with the toxic agent and with the lesions determined by this in the organism, modifications which are endowed with teratogenic power much superior to that of the blood of healthy individuals, and capable of having an influence on the development of the product of conception. The experiments have been done with the method of intra-albuminous injections into the eggs of the hen

With a new series of experimental researches he studied also the direct influence which pellagra exerts on the procreative power, using hens as experimental animals, slowly intoxicated with feeding of spoiled maize, and saw that the power of proliferation not

only in regard to its duration, but also in regard to the number of the products of generation, was reduced, that such nutrition brings modifications to the ovum and to the spermatozoon before their union, which modifications manifest themselves subsequently in the abnormal evolution of the embryo this (abnormal evolution) then consists in a congenital exhaustion more or less accentuated and precocious of the vitality of the product, and hence in a general retardation in its evolution, or in early death, and in the gravest cases in partial death of the germ, only the blastoderm developing itself, and even in total death, in which case is included also this last. The anomalies, hereditary in the true sense of the word, consisted in partial arrests, and sometimes total ones of the primitive vesicle of the cephalic extremity (anencephalia) with enormous development of the ocular ones (macrophthalmia), in punctiform hemorrhages localized specially in the cephalic extremity of the germ, this fact being united (a) to an abnormal state of all the primitive circulatory apparatus, (b) to a greater fragility of the walls of the vessels, or at least (c) to a disproportion between the blood-pressure, and the resistance of the walls themselves the vessels in fact presented ectasiae, varicosities with hemorrhages and extravasations of various degree. Under multiform aspects this is an important fact—the frequency with which the anomalies of development, the monstrosities were related to the cephalic extremity, deviating the evolution of the primitive central nervous system. By reason of all this, it remains demonstrated that

the maldic poisons, which circulate in the organism of the parents, specially of the pregnant one (gestante), are capable of determining (a) a precocious state of exhaustion of the product of conception, which explains to us the frequency of the interruption of the pregnancy, and of the death of the fetus, and (b) again grave deviations from the typical form of embryonic evolution, giving anomalies, important monstrosities which we encounter frequently even in man, and (c) finally, that that predilection, which the toxic element shows for the central nervous system after birth, is observed also on the primitive elements of this, whereby the *pathogenesis* of certain congenital nervous forms, such as spastic paralysis, hydrocephalus, meningitis, encephalitis, microcephalus, etc., which present themselves in heredo-pellagrins, receives thus exhaustive explanation.

But in addition to these facts, which can be established with our means of investigation, other anomalies and alterations will certainly take place, which it has not yet been given to us to know in their intimate nature by reason of the insufficiency of our studies, and of the means at our disposal, which (other anomalies and alterations) will determine the organic predisposition, the receptivity to morbid forms, general and special, systemic, localized, in infancy or in the adult, according to the intensity with which they acted and modifications which they brought into the organs and into the systems.

*Simonini* (1905) admitted that the maternal maldic intoxication has af-

fects the foetus, giving arrest of development of the nervous centers and perhaps also determining the lesions of the cerebral and spinal meninges.

Discussing heredity, he asks "in what consists this hereditary predisposition, so difficult to define?"

"(a) From the one side one can conceive it as an arrest, an evolutive regression of a tissue, of organs, and of a whole system, which for this reason are more susceptible to new morbid stimuli, and less fit to react; (b) on the other hand this (hereditary predisposition) is certainly connected with toxic and infective processes.

"In a general way, one can consider demonstrated that these processes of infection and of intoxication in the parents, especially in the mother during the period of the gestation, are cause of retardation of the development of some tissues, and sometimes also of arrest and of various alterations which, although cured, appear in relation with morbid forms, which are verified in the extra-uterine life, as happens for some degenerative neuropathies. Nor can pellagra be withdrawn from these general laws, whether it depends on an infective or a toxic process; and hence it is necessary to admit the predisposition, the heredity, the degeneration, which induces in the descendants who are born with the easiest tendency to fall sick of the same affection, and of those pellagrous forms, which the parents themselves had manifested."

*Ugao-Norillo* (1905), in his thirty-six years of experience, has recorded only two nurslings, who received breast milk, complemented with maize,

where a diagnosis of pellagra was clear

*Merk* (1909) states as follows: "If I summarize all these statements of *Gemma's*, then I regret only too keenly—and I hope the majority of the readers are with us—the effort for exactness corresponding only half way to his zeal for the subject. In the year 1871 one must already have had fever-curves, or at least degree-statements, body-weight-determinations, number of the pulse, of the respiration; more exact communications concerning the nourishment and similar matters can be expected. One dare not forget that the treatise gains significance through the circumstance, that the journal, in which it is published, was edited by one *Gaetano Strambio*, a name which through two generations has played an eminent rôle among the pellagrologists of the Lombards. The multitude of physicians, who consider science as something which has *become*, but never as something which is *becoming*, who work only with completed results, is led by such apodictic delineations to inexact diagnoses, and thereby suffers not only the study of this devastating disease, but also mankind itself, because the authorities, supported on the statements of such physicians, squander precautionary measures against pellagra, where no pellagra exists.

"When one thinks that *Gemma* set himself the task of delineating the pellagra of sucklings and of small children, that therewith according to his own words he wished to work out something new, then one must be astounded, that he has not given any word at all of the differential diagnosis

so important in case of such vague symptoms, that he has satisfied himself with saying "For me it is pellagra!"

"A specially strong link in the chain of Gemma's proofs seems to lie in this, that the diarrheas and other symptoms of his "hereditary" pellagra were cured according to *Lombroso's* method on administering arsenic or quinin-arsenic

"Gemma's blind confidence is the more surprising, as he does not trouble himself about the literature up to *Lombroso's* treatise and his own publications, although precisely then the question of heredity, as well as the question of pellagra in case of children was still discussed in lively manner. This is true among others also of his nearest countrymen in Milan

"But from grounds of general natural history sort, I cannot myself decide as to the conception of such heredity of pellagra, and point out this, that kindred equal relationships, as life-manner, life-customs, climatic relationships, only too easily simulate heredity and hereditary tendency

"Before I set myself to the epicrisis of this case so especially rich in suggestive and instructive details, it is still necessary, in order to suppress every doubt in what follows, to determine whether it has here been really a question of pellagra

"If I had in the beginning relied on the authority of the above mentioned gentlemen best known to me, who have knowledge of my purpose to evaluate the case in the literature, I can now refer to the delineation of the case itself. It is, if one thinks that it is a question of ambulant material, positively exhaustive. Especially the skin

symptoms bear that striking characteristic, as—in case of this disease (particularly in the culminating state) for every one, who bestows on it only a half-way attentive look,—it is so extraordinarily marked.

"I refer again in summary to these symptoms: rapid onset; erythematous character, long extended course; sharp and outlining limit, hyperkeratosis, predilection-places, as face, back of hands and feet, gray-brown color. Besides come the juvenia of the diagnosis: additional pellagra-symptoms the endemic; the maize-feeding

"Further it is necessary to determine that the child was not sick of so-called "hereditary" pellagra, but of self-acquired pellagra

"I am not in position to state exactly by whom the word—not to say the idea—"hereditary" pellagra was first used in this literature. I can only say that a hereditary pellagra has not been scientifically demonstrated. And farther where always in the pellagra-literature the proof—not the assertion—of a hereditary form is sought so to be brought out, that one is in condition to lay thereon the measuring-rule of a criticism, it is easy for one to determine the incorrectness of this proof"

*Alessandrin* (1910) emphatically states "it has never been given to us to find pellagrous babies. With a limited number of patients, it has not been possible for us to establish whether heredity has had an influence on the development of the disease." However, in another paragraph I have found the statement "because in the same family where the components, more or less, must undergo the sad



consequences of unfavorable hereditary, hygienic and dietetic conditions and of excessive labor, only a very few members (one or two, rarely more) fall sick."

*Mane* (1910) believes that at times the disease is hereditary and that the children of generations of pellagrins are frequently feeble in resistance

Though *Samson* (1910) does not accept the disease as hereditary, he believes, however, and advances the idea that "the infant can contract the disease 3 to 11 months after its birth, a fact which he explains thus. the mother carries the infant with her to the fields at the time of agricultural labors, and it is there that *simulium reptans* inoculates into this last the morbid germ"

*Mane's* "Pellagra" (1912) "Most authors agree that the disease does not occur in infants unless they are fed on spoiled corn."

*Snyder* (1912) in accumulated data received in answer to letters addressed by him to sixty physicians who, for the most part, had had wide experience with pellagra in this country, summarizes the sixth question—Do you regard heredity as an etiologic factor? Why?—"Regarding heredity, all answers but six were negative. These six expressed the opinion that heredity should be considered, but only insofar as a weakened constitution inherited from pellagrous parentage might predispose to the disease"

*Tamboni* (1912) acknowledges, with limitations, heredity in pellagra. "Pellagra would transmit itself only when it is in activity (in other words, when it is in activity, that is, when there

exist manifest phenomena—nervous, cutaneous, gastro-enteric, etc. In the moments of truce, on the contrary, when the pellagra is found so to speak in the latent state, as is the case most of the time, the infant would be born immune"

*Franchetti* (1913) boldly asserts "as a conclusion of all the amount of work done one can affirm that a sure case of pellagra among nursing infants has never been observed, and that the few cases recognized all refer themselves to infants of age over one year, and in whom one was not able, with certainty, to exclude the influence of maidic feeding. In fact, none of the authors who have studied the disease, from the most ancient to the most recent, has ever had to infer that pellagra had a predilection for individuals of tender age." He goes on further to state—"it would have been very strange, that all the forms of infantile pellagra should have constantly escaped observation, unless one wished to admit in them a particular difficulty of diagnosis" Perhaps *Franchetti's* admission is responsible for failure of diagnosis in children, as he compliments *Samson* in the latter part of his article regarding the ability of the former to be able to affirm the frequency of pellagra in infants. For instance, he cites statistics, 1911-1912. In 22 provinces there were only approximately fifteen cases of pellagra in infants, though the number of cases reported were in excess of 20,000

*Peroncito* (1913) states "results equally interesting are had from an inquiry regarding the single cases. For example, the most frequent, the

case of families in which, following altered economic conditions, there have manifested themselves suddenly new cases of pellagra, sometimes even several contemporaneously and specially in *babies*"

*Agnostini* (1913) interestingly states "while in opposition to that of healthy families the birthrate of pellagrous families is but little removed from theirs,—in these (pellagrous families) the figure of the mortality is truly impressive, as it exceeds the double of the common average

"It is generally in the first three years of life that the offspring of pellagrins die marantic through chronic gastro-enteric catarrh, and often with eclamptic phenomena

"The sucklings of pellagrous mother all have the same physiognomy which strikes one painfully by its suffering and oldish aspect, by the impressive thinness of the extremities. Born hypotrophic, with a weight and a length of body much below the average, they have an incomplete and very slow growth, so much so that at 3, at 4 years of age, they do not succeed in standing on their feet, they stammer a few syllables, the dentition has barely begun. A voluminous head of the pseudo-hydrocephalic type, badly shaped, with the fontanelles open up to 6 or 7 years of age, surmounts a rachitic little face, and raises itself badly on the neck, slender by reason of the hypotrophic and often atrophic thyroid. The thorax with the prominent sternum lets be discovered the costal arches distended below by the swollen and batrachian abdomen, with the umbilical cicatrix projecting. The

delicate extremities with the hypotrophic musculature are in marked contrast with the enlarged articulations. The skin of yellowish color, wrinkled and dry in the face, is often edematous in the face. The lips are violet and present easy ulcerations; the tongue is large and catarrhal, they ordinarily have diarrhea and gastric and intestinal dilatation.

"They are sad, querulous, insatiable, and rest little at night. This is the physiognomy common to these miserable ones, who—in the blood and in the maternal milk—find the deleterious principles which enfeeble the evolutive potentiality of their organisms.

"As for the milk of the pellagrous mother, I have verified it as insufficient in quantity, deficient in quality. From various analyses made, I have found that the apparent composition of the milk is not far removed from that of normal milk, except for an increase of salts and a diminution of casein, but without doubt there must pass into the milk those toxic principles circulating in the blood of the pellagrins, which determine the chronic catarrh of the digestive routes, the onset of convulsive phenomena. They contribute besides to the production of these phenomena, and to the defect of the nutrition, (contribute) to the scantiness of milk secreted, the prolonged nursing, the precocious and incongruous feeding of the sucklings.

"A clinical fact of the greatest interest has proved to me that the pellagrous intoxication of the father can influence in sinister manner the product of conception even if the mother is immune from pellagra. A healthy and robust peasant woman

(contadina) of the Reatino has for husband an individual affected by grave pellagra. of three offspring, two have died after a few months of life from eclampsia. The third, a daughter still living, is three years old, while she has the aspect of a six months infant, weighing only 5 kg., and being 60 cm long. The signs of the dystrophies of the tissues, and of the retarded development, are most accented.

"The head, which supports itself badly on the delicate neck, is asymmetrical and hydrocephalic, the face tumid, yellowish and oldish looking: one notes absolute lack of teeth, the thyroid body is atrophic, the abdomen swelled, the extremities delicate, the articulations enlarged. She has already been stricken twice with convulsive phenomena. Those among the born-pellagrous who survive the period of nursing are differentiated from normal children (a) by the disproportion between the age and the wretched development of the body, (b) by the late and uncertain walking, (c) the easy timidity, (d) the sad and suffering aspect, (e) the profound oligemia, (f) the yellowish skin often edematous and fissured on the back of the hands and of the feet, (g) the mucosa of the lips, violet and ordinarily ulcerated

"Together with (a) the bad cranial conformation, (b) the asymmetrical face, (c) the slender and badly proportioned extremities, (d) the muscular atrophy,—is notable the projecting of the epigastrium and the swelling of the abdomen by reason of the dilatation of the stomach and of the intestinal loops. They eat with voracity, they complain of a sense of weight

and of burning in the epigastrium, the salivation is troublesome and persistent, the chronic catarrh of the digestive routes is frequent and rebellious to remedies. One notes retardation of the speech center, ordinarily the psychic functions are slow, and scantily developed. They are melancholic, cry easily, and complain of continual sufferings.

"In the cases in which the pellagrous hereditariness from generation to generation cumulates and aggravates itself, these phenomena of physical and psychic degeneration reach the outside limits of idiocy, of nanism, of sexual dystrophy. The clinical types illustrated by me demonstrate this, in whom the arrest of development was so complete that at 18 to 20 years of age they presented a stature which did not exceed the metre, and the persistence of the fundamental physical and psychic characteristics of infancy. The importance of these cases stands also in the *fact*, that these forms of dystrophic infantilism, of myxedematous idiocy, in which together with the most marked arrest of the development, with the complete absence of the piliferous system, there is a sexual dystrophy so conspicuous as to present the penis and the testicles like those of a newborn, had not previously appeared in the families of the pellagrins of Umbria. In the cases in which the danger of infancy is survived, there continues in adolescence and in young the same retardation of the organic evolution; the muscular weakness persists, the oligemic state, the hypotrophy of the tissues, and there is a notable retardation of the approach of puberty.

"From the statistical data collected by me, it results that the majority of the heredo-pellagrous children (fanciulle, girls) do not menstruate until they are 18 years of age, and the appearance of this is accompanied by vertigines, headache (cefalea), pains, is irregular and often substituted by troublesome leucorrhea. The slenderness of the extremities, the scantiness of the fat, the profound anemia, the lack of harmony of the lines of the face of the person, take from these unfortunates that attractive aspect which in the most beautiful period of life is the sole appannage of the daughters of the poor man. In the males we have ordinarily a stature inferior to the average, and extremities badly proportioned.

"In expectation that the law against pellagra may come, however opportunely modified, to prevent the diseased of pellagra increasing further, it is necessary meanwhile and quickly to provide for this, that the pellagrous women during the last period of gestation are re-invigorated with a suitable alimentary treatment, or removed at least in that time from the deleterious action of the toxic principles of spoiled maize. The nursing of the offspring ought to be as a rule forbidden to women affected by pellagra. But the gravest difficulty which in practice the actuation of this provision would encounter, counsels a modification of the postulate in the sense of assuring to the nurse at least during nursing a feeding healthy and sufficient. This can be done by means of the aids of nurse's pay (*bahatico*) in the places where it may not be possible to send these patients into the pellagrosaria.

The pellagrosaria in my opinion, ought to have special sections for refuge of the pregnant mothers and of the nurses.

"I have also noted in the families attacked by pellagra for the first time, ordinarily the adults and the old fall sick—in the families in which the disease is hereditary, there are observed cases of intoxication not only in the adolescents, but also in the infants of tender age.

### *"Conclusions*

"1—The maidic intoxication of the ancestors and specially of the mother in the period of gestation and of nursing, induces in the offspring a precocious exhaustion of the vitality, a more easy morbidity, retardations, deviations, and sometimes arrest of the development of the body up to the last degrees of somato-psychic degeneration, to idioy, to nanism, to sterility.

"2—The heredo-pellagrins present a special disposition to contract pellagra and speedily pellagrous insanity. In addition, pellagra figures frequently as unique factor of constitutional neuropathies and psychopathies.

"3—Such slow and progressive hereditary degeneration, has already induced an evident and notable imperfection in the organisms of the rural populations in the zones in which the pellagrous endemic is more inveterate and diffuse. From this (the pellagrous endemic) (a) the elevated percentage of the mortality of those born heredo-pellagrins, (b) the continuous increase of the individuals—weak, dystrophic, sickly, incapable of military service, powerless to sustain the fatigues of the camps, fatally destined to populate

the refuges of beggary, the hospitals, the insane hospitals, with economic and social damage, progressive and incalculable "

In 100 heredo-pellagrous children under 20 years of age, he reported to have found 34 already attacked by pellagra, and with prevailing alterations of the nervous system and 15 of these were under 10 years of age. Of the 225 pellagrins up to the present time brought into the pellagrosarium of Citta di Castello, 73 are under 20 years of age, and of these (73), 21 are under 10 years of age

*Raubitschek* (1915) writes: "But it is certain that in the better works of the last few years the belief is clearly expressed that even in pellagra regions not all individuals living under the same relationship succumb to the disease in equal manner. Aside from this, children, in general, seldom fall sick of pellagra; indeed infants remain exempt (perhaps in consequence of the nourishment with mother's milk and continuing same over a period of years); rarely seen in the first ten years, if the writings of *Fritz*, (1912), *Merk* (1909) and *Christoforetti* (1905) are correct."

*Niles* (1916) expresses the belief that heredity as a predisposing factor seems fairly well proved. He has records of 81 instances where pellagra was observed in the second or third generation and at present has under observation 28 cases where pellagra has occurred (most fatally) in the parents or grandparents. One instance, where an infant was born of a pellagrous mother, was reported. It seemed that conception took place during a re-

mission of the disease, but the confinement came on during the recrudescence. The infant lived only 2 months, never thrived and its skin was harsh and dry during the whole of its brief life.

*Muncey* (1916) in a very creditable study of the heredity of pellagra, concludes "that the data collected shows no evidence of direct heredity. There may, however, be an hereditary predisposition to the disease in those families in which chronic gastro-intestinal symptoms have existed for several generations. The relatively high proportion of gastric and intestinal diseases among pellagrous families would seem to substantiate this hypothesis."

*Rice* (1916) mentions as one of his conclusions, in a very systematic study, that "hereditary weakness was one of the predisposing factors operative in this series of cases "

*Davenport* (1917) believes "that pellagra is not an inheritable disease in the sense in which brown eye color is inherited. The course of disease does depend, however, on certain constitutional, inherited traits of the affected individual "

*Murphy* (1917) states that pellagra is neither hereditary nor transmissible from mother to nursing infant.

*Harris* (1919) in perhaps the most complete textbook written in the English language written on the subject of pellagra, mentions. "As to whether the malady is transmitted directly from parent to offspring we are still not in a position to determine, though the author is strongly of the opinion that this is the case. That deleterious in-

fluences are directly inherited where the parents suffer from the disease is clearly indicated by the fact that the offspring frequently exhibits physical malformations, curious asymmetries in the nervous system, and in a great number of instances early shows constitutional deficiencies, all of which can be explained but in one way. Assuming the truth of the author's thesis, that practically all of the pronounced clinical manifestations of this disease are the result of organic change, there can be no reason, *a priori*, why such alterations may not occur during embryonic life, and why pronounced symptoms of pellagra should not develop in infancy,—particularly where the child has not been properly nourished or has suffered from acute infectious processes. While it is true that we have no direct observations bearing on this point, the author feels under the circumstances that the view just expressed may be tentatively advanced, not only as an explanation of the typical pellagrous attacks in children, but of the other symptoms of ill health that the offspring of pellagrins so often exhibit, and to which attention will be more particularly directed in the succeeding pages."

*Voegtlin* and *Harris* (1920) preface their fourth article as follows: "Pellagra occurs only rarely in nursing infants, but undoubtedly the disease does sometimes appear during the first two years of childhood. The literature on pellagra contains a few brief references to this subject."

Later they described "the case of a breast fed pellagrous infant, five months of age, whose mother was evi-

dently free from the disease, the explanation of this particular case being on the basis of the vitamine hypothesis. In this instance, the mother living on a one-sided diet, may have retained enough vitamins for her own metabolism. Her milk, however, may have been deficient in this respect, with the result that her infant developed the disease."

*Goldberger, Joseph, Wheeler* and *Sydenstricker* (1920) state "the disease is rare at the age of 2 and under."

*Mitchnik* (1911) fails to state his opinion regarding hereditary pellagra but mentions, "among pregnant women, pellagra causes, as a rule, abortions, and when they have infants, they are sickly and degenerated."

*Fritz* (1896) calls to our attention "the pellagrosarium (Inzago in Province of Milano) has been open for 15 years, and the pellagrins received and treated are 1,285. Of these, with the exception of 40, all show the congenital pellagra constitution; the greater part from the paternal side, and with long scale ascending into the ancestors."

"Pellagra continues in those families which for years and years have been desolated by it, and those are the families in which the conditions alimentary, hygienic and of the artificial surroundings respond most to the causes of the fatal disease in those families which are refractory to advice, to suggestions, and who wish to continue according to the measure of the past, even if it is deleterious and injurious."

*Mandolesi*, in a report made to one of the Congresses, said: "In some localities, where up to a few years ago pellagra was confined among those of advanced age, it has now rapidly involved also the youngest organisms"

Among some of the lesser authorities favoring hereditary pellagra may be mentioned *Maraglio* (1882), *Maragliano* (1879), *Gmtrac*, *De la Fautrie* (1805), *Thuene*, *Babes* (1900), *Natalita*, *Ronconi* (1890), *Devoto*

(1901), *Lavacher* (1905), *dell 'Isola* (1902), and *Lucantello*.

There is a smaller group who dispute the theory of inherited pellagra—*Facheris* (1804), *Winterlitz* (1862), *Solar* (1741), *Fournier*, and *de Giovanni* (1824) The contributions of the latter group, in particular, as well as those mentioned above, are not based on the number of cases or studies that would justify conclusions affirming or denying the hereditary nature of this disease.

## Editorials

### *THE RELATION OF IODINE DEFICIENCY TO GOITER*

If any theory was ever accepted as a positively demonstrated fact, that of iodine deficiency as a cause of goiter has surely been accepted as beyond any question by the majority of the medical profession of the world and particularly by that of America. The writings of Marine, Kimball, Plummer, and others, have so impressed this view upon the American Medical and lay minds that any dissenting view from that which regards a deficiency of iodine as the cause of simple colloid goiter must surely be regarded as a rank heresy. Nevertheless, the old infectious theory still has a few adherents, as does also the view that there are other factors concerned in the etiology of goiter besides a lack of iodine in the food or drinking water. In an article in the November Annals, Marine believes that in addition to an absolute iodine deficiency as a cause of goiter, there may also be factors bringing about a relative iodine deficiency by increasing the needs of the organism for thyroxin. Among the more important of these factors he mentions food, pregnancy, infectious diseases, and puberty. In winter cabbage there is found a stable goitrogenic substance, in summer cabbage an unstable anti-goitrogenic substance. Neither substance has yet been isolated. That

there would appear to be some other factor concerned in the etiology of goiter besides a simple lack of iodine is indicated by the fact that there are regions in the world especially rich in iodine content, and yet goiter occurs in such regions. The inhabitants of the Vistula delta live in such an iodine-rich country. They excrete large amounts of iodine, their blood-iodine is double that of the normal, their food contains 8-10 times the necessary amount of iodine; and the thyroids of these regions have a much higher iodine content than the normal amount of 3-6 mg; and in spite of this superabundance of iodine, goiters occur. According to Liek, there has been since the War an increase in goiter in this region, although no apparent change in the food content of iodine has taken place. Further, in this region iodine has no specific action against goiter. Moreover, Oswald has shown in mountainous regions of endemic goiter that some thyroids, in spite of the iodine deficiency in food and drinking water, have the power of combining large amounts of iodine, so that some goiters possess a relatively high iodine content. Hellwig of Wichita, Kansas (Klin Wochschr, October 11, 1930, p 1913) has approached the problem experimentally, using rats as the classic animal for thyroid experiments. He found that rats fed for 160 days upon a diet deficient in



iodine showed atrophy of their thyroids instead of the compensatory hyperplasia described by other investigators. The poorer the food in iodine, and the longer such iodine-poor diet was given, the more marked the degree of thyroid atrophy. Hellwig regards this as proving the correctness of Wegelin's view that atrophy and not hyperplasia of the thyroid is to be expected, when iodine, the activator of the thyroid function, is deficient in the food. Without denying the prophylactic effects of a high iodine-content in the food in the genesis of goiter, Hellwig holds the view that endemic goiter is by no means proved to be of the nature of a compensation for the iodine deficiency; but he is convinced that the true cause of goiter is one, or several, positive factors. He finds this in the high calcium content of the drinking water of the goiter regions. More than fifty years ago this view was advanced by McClelland, Boucharlat, Billiet, and Boussingault. More recently Pighini and Abelin, who demonstrated an antagonistic action between calcium and thyroxin, have pronounced in favor of this theory. Wilms and Repin demonstrated that goiter-water lost its strumigenic effect in animal experiments when the calcium salts were precipitated by concentration in a vacuum. Geological investigations by McCarrison in Chivral, and Gilgit in Northern India showed that the richest goiter regions were associated with limestone formations. Also Tanabe produced the most marked goiters in rats on an iodine-poor diet, but which were given at the same time water rich in calcium. Hellwig studied the influence of water rich in

calcium on white rats maintained on an iodine-poor diet. In all of the rats so treated the thyroids showed significant enlargement and hyperplasia. Microscopically these goiters presented the appearance of a pure epithelial hyperplasia. Hellwig regards the positive factor to be the high calcium content of the water. When associated with iodine deficiency, the thyroid responds with the more intensive degree of hyperplasia—the parenchymatous goiter—when the food is rich in iodine, the excess of calcium leads to the production of a diffuse colloid struma. Hellwig apparently sees no essential difference between parenchymatous and colloid goiter; the two forms according to his opinion represent simply different degrees of reaction of the thyroid to the same goiter-producing agent with different iodine-content of the environment. In other words, colloid and parenchymatous goiter are both due to a single specific cause (calcium); the kind of goiter is due to the iodine-factor; parenchymatous when iodine is lacking, colloid when iodine is abundant. The weak point about this view is that Hellwig apparently has no conception of the constitutional factors underlying Graves' syndrome, and that the part played by the thyroid in Graves disease is a purely secondary one, and that the pathologic constitution remains even after thyroidectomy. Without the constitutional anlage there can be no Graves' disease. The great problem is what is the relationship between the thyroid and the Graves' constitution? The solution of this is not so easy as the article by Hellwig would indicate. Colloid goiter and parenchymatous goiter

cannot be different degrees of reaction to the same specific cause. The Graves' constitutional is congenital, familial, and hereditary. Upon this constitutional foundation an abnormal hyperthyroidism may or may not develop. When it does, Graves' disease is the clinical result. As Moschcowitz has recently pointed out, the cause of this hyperthyroidism is usually psychical trauma. But the pathologic picture in the thyroid underlying the full-blown Graves' disease is that of a parenchymatous goiter. And this is always associated with the general pathologic features of the thymico-lymphatic constitution. This extremely important fact would seem to have escaped Hellwig's attention.

#### THE ROLE OF STREPTOCOCCUS HEMOLYTICUS IN SCARLET FEVER

The problem of the etiology of scarlet fever and the rôle played therein by *Streptococcus hemolyticus* still seem far from being settled, according to the Report of the Health Committee of the League of Nations, and much experimental work carried out during the last three years. Specificity of the Dick toxin has been questioned or denied by numerous investigators, among whom may be mentioned Burgers, Cooke, van Groer and Redich, Friedemann, Meyer, Molkte, Paris and Okell, Smith, Wheeler, Wadsworth, Zlatogoroff and Derkatsch. Ciuca and Satake were unable to produce experimental scarlet fever in a large series of Dick positive human volunteers by swabbing or injecting their tonsils with freshly isolated cultures of scarlet fever streptococci or scarlet fever

blood. The serological specificity of *Streptococcus scarlatinae* is not granted by Burgers and Wohlfeil, Ciuca, Friedemann, MacLachlan and Mackie, Smith, Wordsworth, Williams, Zlatogoroff and Derkatsch, and numerous other investigators. The failure of the scarlet fever antitoxin to abate septic complications is generally admitted. Because of these discordant results and the apparent lack of agreement with the group maintaining the streptococcus etiology of scarlet fever, the filterable virus theory of this disease has again been brought to the fore. Zlatogoroff claims to have demonstrated that during the incipient stages of scarlet fever there is a filterable virus present in the faucial exudate which is capable of activating the otherwise ubiquitous and avirulent hemolytic streptococcus to take on toxigenic and pathogenic properties by which the clinical picture of scarlet fever is produced. When injected either intravenously or subcutaneously in rabbits, monkeys, and man, the filtered and sterile scarlatinal exudate almost constantly produces the scarlet fever syndrome, with typical histopathological lesions, as well as changes in the blood picture, analogous to the epidemic form of the disease. The experimental disease confers immunity for over two and a half years against reinfection. In rabbits and monkeys the virus alone is capable of producing the diseases in the absence of hemolytic streptococci, and yet, upon recovery, the blood-serum contains agglutinins for hemolytic streptococci. When suspended in Ringer's or Locke's solutions this filterable virus resists dispersed sunlight for 33 days at room temperature, and remains active for 35

days when left in the dark. In 0.5 percent phenol it remains viable for 15 days, and heating for 1 hour at 60°C completely destroys it. Birkhaugh, Ackerman, and Allen (Proc. Soc. f Exper. Biol and Med, Nov, 1930) attempted the production of the scarlatinal syndrome with whole and filtered scarlet fever faucial exudate from early and moderately severe cases of scarlet fever, according to the method of Zlatogoroff. From this experimental investigation, they concluded that sterile filtrates of scarlatinal faucial exudations failed to produce the scarlatinal syndrome in guinea pigs and rabbits. Subcutaneous inoculation of the unfiltered scarlatinal faucial exudations into guinea pigs and rabbits produced irregularly an erythema suggestive of scarlet fever, without any remarkable changes in temperature, leukocytic cell count or differential blood picture. Development of marked skin sensitivity to the Dick toxin following the injection of scarlatinal exudations suggested an allergenic basis for the suggestive scarlatinal rash which was followed by desquamation. Monkeys remained entirely refractory to the scarlatinal faucial exudations. A filterable virus in scarlatinal faucial exudations capable of producing the scarlatinal syndrome in guinea pigs and rabbits was not demonstrable. These investigations are, therefore, directly contradictory to those carried out by Zlatogoroff; it is difficult to explain such contradictions in the hands of apparently reliable investigators. Birkhaugh, Ackerman, and Allen's work confirms our results that may be used against the Dick hemolytic streptococcus

theory. If anything, they rather tend to support it.

### *THE CAUSE OF GINGER PARALYSIS DEFINITELY IDENTIFIED*

The cause of ginger paralysis has been determined. This paralysis, which has afflicted thousands of victims, is not caused by ginger at all, but by a compound known to chemists as tri-ortho cresyl phosphate. This chemical is the main constituent of technical tricresyl phosphate, which is widely used in trade circles, especially in the manufacture of varnishes, shellacs, and similar preparations. Being cheap and readily obtained in any quantities, it appears to have been used by irresponsible makers of so-called ginger extract to replace the ginger. There seems to be no question that the adulterated paralytic ginger extract contained tri-ortho cresyl phosphate in an approximate concentration of about two per cent.

The United States Public Health Service has been working on the public health aspects of "Jake paralysis" since the wide appearance of this condition in certain sections of the country last Winter and Spring. In attacking the problem, it soon became evident to investigators that they were dealing with a new form of paralysis and one in which many possibilities were involved. As the investigations proceeded, it became evident that some form of phenol was the causative agent. Soon attention was centered on technical tricresyl phosphate. Chemists of the Prohibition Bureau had found similar substances in suspected extracts. A number of different

chemicals enter into the manufacture of this commercial product, it became necessary to separate them and find out what effect each might have if used in a beverage. This has been done and it has been found that tri-ortho cresyl phosphate either itself or in combination with other chemicals of harmless nature, when given to various kinds of animals will produce exactly the same kind of paralysis as that caused by drinking of "Jake". The Public Health Service has no record of a single case of paralysis caused by ginger preparations manufactured by reputable pharmaceutical concerns. Tri-ortho cresyl phosphate is, therefore, definitely established as the specific cause of the cases of so-called "ginger paralysis".

Studies conducted on laboratory animals show conclusively that a paralysis of the extremities can be produced uniformly in monkeys and other animals by the injection under the skin or by oral administration of the chemically pure as well as the technical tri-ortho cresyl phosphate. The failure to produce any symptoms, whatever, in monkeys with enormous

doses of this poison given by mouth indicates that it is practically not absorbed from the intestinal canal in that species.

The precise reason for including this remarkable substance as one of the ingredients of a substandard fluid extract of ginger made and sold for beverage purposes will probably never be known, unless a confession is wrung from the guilty ones. It seems entirely reasonable, however, to suppose that it was included on account of its physical or other properties which make it difficult to distinguish from the normal ginger constituents. Only a chemist of considerable ability could have thought of this, and had there been anything known about the pharmacologic action of this substance and the possible dire consequences, it is probable that it would never have happened. From this the question naturally arises as to whether there are not many other organic compounds of great medicinal interest, perhaps some with great possibilities for the treatment of disease, awaiting the attention of investigators.

# Abstracts

*Treatment of Peptic Ulcer with Gastric Mucin* By SAMUEL J. FOGELSON (Introduced by A C Ivy), (Proc of Soc f Exper Biol and Med, November 1930, p. 138).

The capacity of mucus to lower the free acid in the stomach is frequently suggested in the literature on gastric secretion. Lim determined that the concentration of the mucus in the stomach is highest at the lower secretion rates. The present problem was to determine the effect of increasing the mucus content of the stomach upon the free HCl. To evaluate the antacid effect of gastric mucin, it was necessary to either stimulate the secretion of mucin or to administer mucin by mouth. In these experiments attempts at stimulation failed to give consistent results, therefore a neutral preparation of hog mucin was prepared. Two ounces of this mucin in the stomach of Pavlov pouch dogs, after stimulation with 1 mgm. of histamine, was found sufficient to keep the stomach free of free HCl despite the fact that the pouches in these dogs showed adequate gastric secretion. Free HCl would always be present if the same experiment were performed and egg albumin, gelatin or meat substituted for the mucin. When half an ounce of mucin mixed with a pound of meat was fed the dogs, no free HCl was present during an observation period of 5-7 hours. These results suggested the treatment of peptic ulcer with mucin. Since January, 1930, twelve patients with definite ulcer histories and typical x-ray findings of peptic ulcer were made available for study. In addition to the customary bland diet, one ounce of powdered mucin was added to each meal and about 1 gm. of mucin in tablet form was given hourly. All of these patients were relieved of subjective symptoms within three days of treatment, and present these last three months

recurrence of the pain in observation periods extending over 2-5 months. This work is very suggestive of the addition of a useful substance in the symptomatic treatment of gastric ulcer. If the pain of ulcer, which is so important to the patient, and so often controlled with imperfect success, can be overcome by such a simple method of treatment as successfully and completely as indicated by these experiments, the use of mucin in the treatment of gastric ulcer will be of great value. This can easily be tested out by any one having a patient with gastric ulcer.

*The Therapeutic Use of Potassium in Certain Cardiac Arrhythmias* By JOHN J. SAMPSON and EVELYN M. ANDERSON (Proc. of Soc of Exper. Biol and Med, November, 1930, page 163).

The investigation of the action of potassium salts on the heart dates from the time of Ringer's classical experiments on the frog heart. He proved, irrespective of osmotic tension, the necessity of sodium potassium and calcium ions in a balanced solution. Hering stopped paroxysmal ventricular tachycardia and ventricular fibrillation in the dog, and many investigators have similarly obtained immediate cessation of both auricular and ventricular ectopic rhythms by intravenous or intracardiac injections of solutions of potassium chloride. Wiggers suggested the possibility of its therapeutic use in ventricular fibrillation of accidental electrocution. It thus seemed reasonable to attempt to disturb the calcium potassium ratio in favor of potassium for certain other therapeutic reasons. Potassium salts were, therefore, used clinically to check attacks of paroxysmal ectopic ventricular tachycardia, and to prevent the occurrence of auricular and ventricular ectopias. Four different solu-

ble potassium salts were used potassium chloride, potassium iodide, potassium citrate, and potassium acetate, all with apparently identical effect. It is presumed that the anion and acid-base influences are negligible. For later use, we have employed only the acetate, because it causes no gastric irritability when administered in raspberry syrup or similar menstruum. It was found that potassium may be safely administered orally in doses of 1-5 gm of certain soluble salts, to human cases of heart irregularities. In 12 cases of such oral administration in auricular or ventricular ectopic beats or tachycardias, definite control of the arrhythmias was obtained in 5 cases. In Case No 1, of this series, two attacks of paroxysmal centricular tachycardia, with duration 8 hours and 4 days respectively, were checked within the period of expected absorption time for potassium. Of the remaining 7 cases, 4 were free of any other evidences of cardiac pathology, and of these 4, none showed even a suggestion of any response to potassium. The failure to affect this group may be used to differentiate such patients from those with true myocardial damage. A low potassium content of myocardium is known to exist in cases of heart muscle failure, and may be the explanation for this difference in response. The influence of potassium on the arrhythmia occurred in 30-90 minutes after administration and the necessary dose varied in different individuals. The effect was maintained from 6-8 hours, and occasionally some effect was observed for the succeeding 24-48 hours. A definite effect on the electrocardiograms in certain cases after potassium administration was observed. Certain ill effects are occasionally noted, namely gastric distress and diarrhea. The acetate and citrate caused less distress than the chloride or iodide. The paroxysmal nodal tachycardia observed in one case, and the epistaxis and petechiae in another may have been due to the potassium administration. The investigators conclude that potassium salt administration by mouth is effective in checking auricular and ventricular ectopic beats and tachycardia in the majority of cases of organic heart disease.

The failure to affect arrhythmias in patients without other evidence of cardiac pathology may be used to differentiate this group from the former. Potassium administration does not prevent the occurrence of auricular fibrillation.

*Pathological Lesions Produced in Rabbits Following Intravenous Injection of Concentrated Scarlet Fever Toxin* By K E BIBKHAUG and R P HOWARD (Proc Soc of Exper Biol and Med, November, 1930, p 95)

In a number of papers Duval and Hibbard have reported the production in rabbits of an acute glomerulonephritis following the intravenous injection of the bacteria-free toxic principle of *Streptococcus scarlatinae*, which they characterized as endotoxic in nature. Their histopathological material was considered analogous to that observed in human scarlatinal glomerulonephritis. These experiments were repeated by Reith, Warfield, and Enzer, who concluded that identical renal lesions occurred in normal rabbits as well as in those injected with suspensions of non-scarlatinal streptococci. They averred that none of the renal lesions produced were typical of human acute glomerulonephritis. On the other hand, Rich, Bumstead, and Frobisher were able to produce glomerular damage in rabbits by the intravenous injection of bacteria-free filtrates of fresh broth cultures of a virulent strain of *Streptococcus viridans* isolated from the blood in a case of subacute endocarditis with renal involvement. Their histological material was typical of acute hemorrhagic glomerulonephritis. The object of the present investigation was two-fold: first, to study the degree of toxicity of the concentrated scarlet fever toxin in chinchilla and mixed rabbit stock, and secondly, to scrutinize carefully the specific destructive action of the concentrated scarlet fever toxin on the rabbit kidneys. Doses of unconcentrated and concentrated scarlet fever toxin varying from 0.05 cc to 10 cc were injected intravenously into chinchilla and mixed breed of stock rabbits. Although the chinchilla rabbits showed a relatively greater

susceptibility to the lethal action of both the unconcentrated and concentrated filtrates, a minimum and specific lethal dose was scarcely discernible either in the chinchilla or in the mixed breed. The doses causing death varied irregularly between 0.6 cc. and 5 cc of the concentrated toxin. The stock rabbits which lived 24 hours after the injection were killed at that time, and studied for macroscopic and microscopic lesions. No remarkable macroscopic lesions were found in any one animal. Although minor pathological differences were observed in individual animals, the histopathologic picture as a whole was uniform, and the differences showed no correlation with dosage, number of injections, or type of rabbit employed. The renal vessels showed a moderate hyperemia, especially of the capillaries and smaller veins. Congestion of the glomerular capillaries was fairly marked in some sections, while only moderately in others. No hemorrhage was observed. The dominant picture was excessive tubular swelling, especially pronounced in the convoluted tubules. The cytoplasm of the latter was markedly granular, and the nuclei were only faintly stained. No definite necrosis not attributable to postmortem changes were seen. The tubular swelling was so severe in several sections that the tubular ends were pushed into the space intervening between the glomerulus and Bowman's capsule. No tubular casts were observed. The glomeruli were in general hyperemic without showing the least trace of hemorrhage. A faint-staining amorphous substance, resembling albuminous exudate, often distended Bowman's capsule. No cellular reaction was found in the interstitial tissue, glomeruli or tubules. The investigator concluded that a minimum and specific lethal dose of the concentrated scarlet fever toxic filtrate was not discernible in rabbits, although the chinchilla breed displayed a relatively greater susceptibility to the lethal toxic effects of scarlet fever toxin. The renal changes observed in the rabbit following intravenous injections of unconcentrated and concentrated scarlet fever toxic filtrate were not those of acute poisoning of glomerular type, but were

rather analogous to lesions observed in milder forms of tubular damage.

*The Blacktongue Preventive Value of Minot's Liver Extract* By JOSEPH GOLDBERGER and W. H. SEBRELL (Public Health Reports, December 12, 1930)

This study had been organized prior to the death of Dr. Goldberger and had been partly carried out under his direction. It has been shown that dogs on the basic blacktongue-producing diet No. 268 develop signs of blacktongue in a period which only occasionally exceeds 53 days. When Minot's liver extract, in a daily dose equivalent to 100 gms of fresh liver was given to 5 dogs on this diet, the occurrence of blacktongue was prevented for a period of at least 185 days. Three of the animals were continued on the basic diet after discontinuing the liver extract; these animals then developed blacktongue in 54, 228, and 52 days respectively, thus further strengthening the presumption that the delaying effect was due to the liver extract. The same quantity of Minot's liver extract, given daily to dogs that had developed signs of blacktongue on the basic diet, caused a recession of symptoms in 4 out of 5 dogs and prevented a recurrence except for slight signs, in two of the dogs for at least 140 days. The period of observation was too short to warrant the statement that blacktongue would not have developed at a later date, and the possibility of fleeting signs of recurrence in two of the dogs may indicate that the quantity given was barely able to maintain the animals. The conclusion is drawn, however, that Minot's liver extract, given to dogs on a basic blacktongue-producing diet, in a daily dose equivalent to 100 grams of fresh liver, has a very definite delaying effect on the occurrence of symptoms, and when fed to dogs in an attack of blacktongue has a very definite curative effect. The most reasonable explanation for this action seems to be that the liver extract carries the antipellagric vitamin with it. In view of the evidence herein presented, it would seem that Minot's liver extract is a fairly good source of the antipellagric vitamin, and given in

larger quantity would be of value as a temporary expedient in the treatment of pellagra

*The Nature of Graves' Disease* By ELI MOSCHCOWITZ (Arch of Int. Med., October, 1930, pp 610-629)

Moschcowitz accepts the constitutional nature of Graves' disease, as described by Warthin, but admitting, as all evidence seems to show, that a constitutional factor forms the background of Graves' disease, the latter is by no means settled by giving a label. The word constitution has a wide connotation, especially in respect to show how far the elements forming such a constitution are congenital, hereditary or acquired. Moschcowitz has no doubt that this constitution is a familial trait and admits that part of the constitution is congenital, as in Warthin's sense. He has, however, no doubt that the psychologic aspects in this constitution are affected profoundly by environmental factors, in most instances by the influence of parents on children. Even if one admits that the neuropathic constitution is the potential of Graves' syndrome, it still remains to be explained why only a small proportion of patients with such constitutions develop the disease while others do not. There must be another factor, and this Moschcowitz maintains is psychic. In four-fifths of the cases fear bears a direct relationship to the onset of the Graves' syndrome. In about one-fifth of the cases a history of fear or sudden emotional crisis cannot be obtained. On deeper questioning it would appear that fear usually accompanies the infection or illness following which the Graves' syndrome has developed. Fear is undoubtedly the basis of most of the factors that have been cited as the cause of the Graves' syndrome. The history of mental trauma is so common in Graves' syndrome that many observers regard it as

a traumatic and anxiety neurosis. There is every evidence that excess of thyroid function represents the predominant evidences of Graves' syndrome. All evidence shows, however, that the hyperthyroidism is secondary and not primary. The characteristic hyperplasia of the thyroid gland in Graves' syndrome is therefore sometimes lacking. The greater preponderance of Graves' syndrome in the female sex is the result of the greater sensitivity of the psyche in the female. The racial incidence of the syndrome conforms to what one would expect of ethnologic sensitivity. It is uncommon in races of coarse mental fiber, and is commoner in those of subtler mental reactions and where the strain of existence is keener. Graves' syndrome is apparently a social disease of the higher civilization. In the development of the influences in which the disorder is likely to develop, religion, the social and political status, the availability of the country for sustenance, etc., are probably important. The relation of the psyche to the development of Graves' syndrome is shown in the rarity of this disease in children, in whom the adjustable reasoning and emotive powers are not fully developed. The determinations of the basal metabolism should not be regarded so much as a diagnostic sign of the Graves' syndrome as a measure of the most prominent symptom, namely hyperthyroidism, and therefore of activity. If the relation of the constitution to Graves' syndrome is recognized it will help to explain the many failures after treatment, whether medical or surgical. This constitution persists after any form of treatment, so that cure is never wholly obtainable. The most profound effect of thyroidectomy is on the basal metabolism. Furthermore, the constitution being profoundly influenced by environment, the treatment of the patient should not cease after thyroidectomy.



# Reviews

*Handbook of Anatomy* Being a Complete Compend of Anatomy, including the Anatomy of the Viscera, a Section of Surgical Anatomy, a Chapter on Dental Anatomy, Numerous Tables, and Adopting the Newer Nomenclature Designated the Basle Nomenclature, Commonly Called BNA. By JAMES K. YOUNG, M. D., F. A. C. S., Late Professor of Orthopedics, Graduate School of Medicine, University of Pennsylvania; Late Associate Professor of Orthopedic Surgery, University of Pennsylvania, etc Revised by GEORGE W. MILLER, M. D., F. A. C. S., Associate in Anatomy, Jefferson Medical College, Surgeon to Montgomery Hospital, Norristown, Pennsylvania Seventh Revised Edition. 460 pages, 154 engravings, some in color F. A. Davis Company, Philadelphia, 1930. Price in cloth, \$4 50

That a seventh edition of this handbook has been called for speaks for its usefulness to students of anatomy. The author's original purpose was to lighten the labors of the medical student, and the editor of the revised edition has endeavored to carry it out. The result is a very concise and complete anatomical compendium, which can be recommended as a very convenient aid to the study of anatomy. The Latinized form of the Basle Nomenclature is used consistently in the text, plates and index. Where both the new and old terms are used, the new is emphasized by its primary position. Some changes have been made in terminology the construction seemed obscure. The book serves well the purpose for which it was intended, and is well recommended.

*George Adam's A Memoir* by MARIE GEORGE ADAM. The author's contributions from the field of pathology and anatomy.

with portrait Constable and Company, Ltd. London, 1930 Price in cloth, \$3 50

This interesting memoir of the life of J. George Adam is the result of the compilation of the main facts concerning his career by his widow, aided by many of his old friends and colleagues. During his long service as Professor of Pathology at McGill University, Adam became widely known and beloved in the States. He was a potent factor in the development of pathology in this country. From 1894 to 1922 he was an active member of the Association of American Physicians, its President in 1912, and contributed numerous papers of value to its programs. His views on medical education had a direct influence on our system of medical instruction. He saw the educational problems from the standpoints of both scientific and practical clinical medicine. His ideal of the proper Medical Faculty was one that would turn out well-trained and capable practitioners, with a training in science and possessing the scientific spirit. He believed in a complete cooperation between the Medical School and the Hospital. He championed the extension of the medical course and the development of five and six year combined courses. As a pathologist Adam was a fore-runner of the present-day conception of Pathology as a biologic science. He broke away from the old-fashioned tissue-pathology, and conceived his science as resting upon the broadest biological foundations. He was far ahead of his times in his views upon bacterial variation and "subinfection." He very early interpreted inflammation as essentially defensive and protective in character. He realized fully the importance of heredity and constitution in disease. He was an ardent follower of Ehrlich, and ingeniously transferred his side-chain theory to the explanation of heredity. As we now realize,

his textbook "The Principles of Pathology" (1909), was an epoch-making work in marking the transition from the old anatomical and cellular pathology to the new biological conception of the present day. In it were foreshadowed many of the chief principles of the medical philosophy of the modern epoch. Adam had also a strong practical side. He was active in enforcing the bearings of pathology on the practice of medicine and public health in its broadest applications. In Canada he was an active leader in anti-tuberculosis work, and in all phases of preventive medicine he exhibited the deepest interest. To those of us who had the good fortune to know him, Adam will always be remembered for his delightful personality, his general culture, and his appreciative spirit. He was a man of wide interests, and possessed of a broad charity, and in his attitude toward life, exhibited the best qualities of a true gentleman of the world.

*Bacteriological Technique*. A Laboratory Guide for Medical, Dental, and Technical Students. By J. W. H. EYRE, M.D., M.S., F.R.S. Edin., Professor of Bacteriology in the University of London, Director of the Bacteriological Department of Guy's Hospital, London. Third Edition. 617 pages, 238 figures. William Wood and Company, New York, 1930. Price in cloth, \$7.50.

The first edition appeared in 1902, and was reprinted in 1906, the second in 1913, and reprinted in 1915. In this new edition the author has incorporated the new and valuable procedures elaborated during the Great War, with the newer methods and media that appear likely to stand the test of time, together with the old and tried methods coming down to us from the pioneers in bacteriologic research. Much space and attention have been devoted to the adjustment of nutrient media to pH standards, and the correlation of these methods with the older titration procedures. Much care has been expended upon the chapters devoted to the chapters on media as a whole, since this section of the work directly affects the efficiency of the bacteriologic laboratory.

The methods applicable to animal experimentation have also been expanded, and the section devoted to bacteriologic analysis has also been extensively revised and somewhat enlarged. This volume presents the subject of bacteriologic technique much more fully than its usual presentation in the ordinary textbooks of bacteriology, and may be recommended as supplementing these, to those engaged in practical bacteriologic work.

*Recent Advances in Chemotherapy*. By G. M. FINDLAY, O.B.E., M.D., D.Sc., Wellcome Bureau of Scientific Research, London. With a Foreword by G. M. WENYON, C.M.G., C.B.E., M.B., B.S., B.Sc., F.R.S., Director-in-chief of the Wellcome Bureau of Scientific Research, London. 532 pages, 4 plates and 11 text figures. P. Blakiston's Son & Co., Inc., Philadelphia, 1930. Price in cloth, \$3.50.

The literature of chemotherapy, which dates from the time of Ehrlich, has now become so extensive that it is difficult for the individual to grasp satisfactorily its significance. With the exception of Kolmer's "The Principles and Practice of Chemotherapy," dealing especially with syphilis, there is no work available in English that gives an adequate survey of the present position of the subject from the point of view of general medicine. Since little progress has been made in the chemotherapeutic treatment of bacterial diseases, and still less in virus infections, the greater part of this work is of necessity devoted to the consideration of the action of chemical agents on diseases due to protozoa, spirochetes, and helminths. It is a relatively simple procedure to determine in the case of these parasites, whether the infection is influenced in any way by chemotherapeutic methods, whereas the detection of bacteria and ultramicroscopic viruses requires more elaborate cultural or inoculative tests. Moreover, these organisms are more easily influenced by chemotherapeutic agents than are bacteria and allied organisms. This book attempts to show the recent advances in chemotherapy. When the last ten years are surveyed as a whole, it is apparent that cer-

tain definite advances have been made in chemotherapeutic treatment, and that a better understanding has been gained of the mode of action of well-established medications. During this period the focus of attention has been shifted from a study of the direct interaction of drugs with infecting organisms to an investigation of the part played by the tissues in chemotherapeutic treatment. This book presents a very good and thorough survey of the literature. The material has been well analyzed and digested, and is presented in a clear and unprejudiced manner. It may be recommended as a thoroughly satisfactory exposition of the subject of chemotherapy up to date.

*Problems and Methods of Research in Protozoology*. Edited by ROBERT HEGNER, Professor of Protozoology, and JUSTIN ANDREWS, Associate in Protozoology in the Johns Hopkins University School of Hygiene and Public Health. 532 pages, 30 figures. The MacMillan Company, New York, 1930. Price in cloth, \$5.00.

This book is the work of twenty-five contributors and two editors. Specialists in the various fields represented have contributed chapters on problems and methods of research in the various phases of the subject about which they were most familiar. The editors have organized the volume with the purpose of aiding both the seasoned investigator and the beginning student. They have attempted to bring together information that is at present widely scattered in the literature or has not yet been published. The field of protozoology has become so highly specialized that each student at present gains a comprehensive knowledge of only one or two groups of protozoa, or of only one or several phases of their host-parasite relations. Consequently it has become difficult for an investigator in one field to keep abreast of the problems and methods of research in other fields. The student who wishes to specialize in protozoology is unable to secure in any easily accessible form an adequate view of the field of such study, its problems available for investigation and of the methods that may be employed in their study. The material

and its treatment make of this book a highly specialized volume not adapted to the use of the ordinary medical student or practitioner. It serves well the purpose for which it was designed, that of giving aid to the special student and investigator in the field of protozoology. Its interest is scientific rather than clinical. Nevertheless there is much scattered through its pages that bears practically upon medicine.

*Diet in Disease*. By GEORGE A. HARROP, JR., M.D., Associate Professor of Medicine, Johns Hopkins University, Associate Physician, Johns Hopkins Hospital. 404 pages, 80 tables, Sample Diets and Food Lists. P. Blakiston's Son & Co., Inc., Philadelphia, 1930. Price in cloth, \$3.50.

This book embraces the material used by the writer in lectures, ward rounds, and clinics to the third and fourth year classes at the Johns Hopkins Medical School on the use of diet in disease. It includes a brief survey of the general principles of nutrition which have particular bearing on clinical dietetics, together with a brief account of the principal foodstuffs and their place in the diet. Long tables of food values have been omitted, as they are obtainable elsewhere, only those have been included of which a working knowledge is of particular value. Some information as to the best methods of preparing certain important foods is also considered useful. Most of the diet lists given have been used in the wards or in the out-patient department of this hospital, and have been tested by trial and experience. Most of the weights of average servings of the foods as given in the food-tables have been redetermined, and in some instances will be found to differ rather widely from figures given in current text-books. The author emphasizes the important fact that some working knowledge of dietetics is necessary to treat disease and to outline diets for the sick. The medical student should have some understanding of the principles of nutrition, but unfortunately he is too often left to his own resources in this matter. He usually finds but upon the complicated diet list which is found in many text-books and which

come discouraged at the hopelessness of committing to memory all of the numerous and often unrelated material. The author also warns against the dangers of following a traditional routine for a given disease regardless of the all important particular needs of the individual patient. Such a procedure may cause positive harm to the patient. Deficiency disorders as a result of improper dietary treatment are not uncommon. Patients with duodenal ulcer may develop scurvy, or patients with nephritis may suffer from protein deficiency. It would be far more useful to give the student a comprehensive knowledge of principles and some idea of the value and use of the foodstuffs which compose the diet. If he masters these elements he is free to formulate his own treatment in the same way that he administers any other therapeutic agent. Not every patient with albuminuria requires a low protein diet any more than everyone with heart disease requires digitalis. The book seems eminently sane, and is clearly and concisely written. He treats of such matters as high protein diet on the basis of facts alone, and not from any preconceived opinion or prejudice. The perusal of this book is recommended to senior medical students, internes, and house physicians.

*Tonsil Surgery* Based on a Study of the Anatomy. By ROBERT H. FOWLER, M.D., Chief Surgeon of the Tonsil Hospital, New York, Junior Surgeon (Throat Service), Manhattan Eye, Ear, Nose and Throat Hospital, New York. 288 pages, 103 illustrations, including 10 full-page color plates. F. A. Davis Company, Philadelphia, 1930. Price in cloth, \$10.00.

This book is written pre-eminently from a surgical standpoint. It is intended primarily for those who seek information on the best types of operation, and knowledge regarding the physical aspects of the tonsil and its attachments as they bear on the operative technic. In it the author presents a hitherto unemphasized phase of tonsil surgery upon which information has been prepared and authenticated so recently that the facts have not been presented in so complete a form before. Through the discovery

made by the author in collaboration with Wingate Todd, of the tonsillopharyngeus muscle and of its relations with the capsule, a marked improvement in the technic of tonsillectomy has been achieved. The new operation removes the whole tonsil in its capsule without trauma to other tissues, and leaves the fossa covered with an intact fascia. On such a surface infection does not spread easily, and the operation is made as safe as possible. This is undoubtedly a great advance in the technic of tonsillectomy. The book is concerned chiefly with the how of tonsillectomy, and not with the why of it. The medical man will find the book deficient in matters of symptomatology, etiology, and pathology.

*Stalkers of Pestilence* The Story of Man's Ideas of Infection. By WADE W. OLIVER, M.D., Professor of Bacteriology, Long Island College Hospital. Introduction by THEOBALD SMITH, M.D., Ph.D., Director, Department of Animal Pathology, The Rockefeller Institute. 251 pages, 23 illustrations. Paul B. Hoeber, Inc., New York, 1930. Price in cloth, \$3.00.

This is a reprint, with additions and corrections, from the *American Journal of Surgery*, Vol. VII, 1929. The volume traces briefly the historical development of man's ideas of the nature of infection and of infectious diseases. Five chapters: Prehistoric Man to Hippocrates, Arabic Medicine, The Medieval Period and the Renaissance, The Seventeenth and Eighteenth Centuries, the Nineteenth Century, and the Twentieth Century are devoted to this evolution of knowledge of parasites and parasitism. The transition from the primitive superstitions and mythologies of the earliest periods through phases of belief in telluric, cosmic, and miasmatic influences, to a final understanding of the living agents of disease is a long and interesting tale and it is very well told by Oliver. The author does not confine himself to his main thesis, his book is a condensed history of medicine as a whole until he reaches the nineteenth and twentieth centuries, where naturally he devotes himself more particularly to his theme. Since infection plays so important a part

in modern medicine, the history of medicine for the last fifty years is concerned chiefly with the development of bacteriology and parasitology, and the secondary branches of serology and immunology. The illustrations are well chosen from the great ones of medicine who have marked epochs of medical thought. The book is a well-written one, it possesses an interesting style, and the facts are told in a clear and concise manner, without vagueness or over-detail. The main facts of this great development of human thought are here, and their evolutionary relationship clearly traced. This is a

good book for the medical student to read while doing his courses in bacteriology. Teachers of bacteriology would do well to include it in the list of reference works to be read by the student, or even to require it as part of the regular work. It is becoming more and more the custom, and a very happy one it is, of tracing the historical development of each subject, anatomy, physiology, pathology, etc., in connection with the regular work in the given line. We suggest that active teachers of bacteriology could make good use of the present volume in the same way.

# BALTIMORE—WHERE WE MEET

(American College of Physicians, March 23-27, 1931)

**A** CITY of active industry and commerce which preserves despite its progress something of an atmosphere of deliberateness—almost conservatism, a city of busy factories, piers, railroad stations, offices, office buildings, shops and markets from which almost every worker goes home to his own hearth,—this, in brief, is Baltimore. Seen from the air, it is for the most part a cluster of flat-roofed dwellings hugging the two branches of the Patapsco River, which

here is nothing more nor less than an estuary of the Chesapeake Bay. Around the winding shore line are miles and miles of wharves, factories and railroad yards. A little farther back from the shore, in a compact group, are the towering centres of the city's finance. Then, surrounding these, lies a sea of homes studded here and there with green islands of park or public square, or with the domes and spires of churches, museums and institutions of learning. And around all these, in



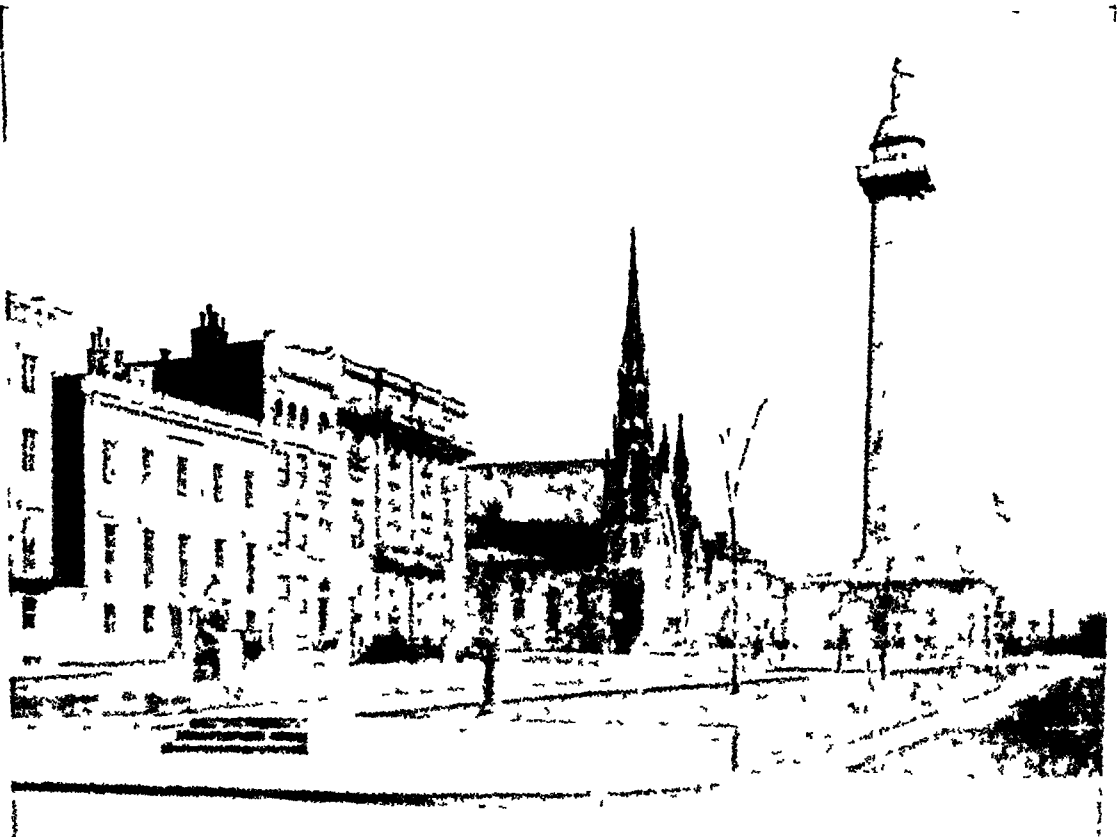
FIG 1 Air View of Baltimore

turn, lie exceptionally lovely suburbs and a rolling countryside which finally merges in the foothills of the Appalachians. Scarcely an American city, unless it be one of the Western Coast, enjoys a more attractive environment. Scarcely a city in the world, unless it be London, disguises its activity so completely, or more deeply impresses one with the sense that the business of the individual is the living of a life rather than the making of a living.

Founded in 1729, Baltimore was named after the domain of the Calverts, the Lords of Baltimore in Ireland. Having lived and grown through the Revolution, the War of 1812, the Civil War, and the World War, the city has, consequently, acquired a rich store of historical connections, many

of which have left tangible memorials behind them. Attached to the streets of the city one may notice the names of Revolutionary heroes—Washington, Lafayette, Pulaski, Greene and Howard. The first monument in the United States to George Washington was erected in Baltimore in 1815. Many years later, in 1924, a bronze equestrian statue to Lafayette, his companion in arms, was placed near the base of this monument, a fitting addition to a section named Mt. Vernon Square, after Washington's homestead.

In the War of 1812, Baltimore gave birth to the National anthem, The Star Spangled Banner. Baltimore "privaters" had played such havoc with the British shipping that Admiral Cockburn determined to exterminate this



"nest of pirates" On September 13, 1814, however, he met a severe defeat off Fort McHenry and was convinced of the folly of this determination. Watching the battle through the night, Francis Scott Key was inspired to write the lines which are now familiar to every American citizen. Fort McHenry dates from 1775. As a unit of defense, it is now obsolete, but Federal and private resources are being expended to preserve and cherish it for its obvious historical value. It lies only a few minutes from the centre of the city on a point of land marking the division between the two branches of the Patapsco.

In the Civil War, Baltimore was regarded as one of the Border-Line cities. Yet, on April 19, 1861, the first blood of this war was shed when a Massachusetts regiment passed through Baltimore on its way to Washington. This was at Camden Station, on the Baltimore and Ohio Railroad, a station which still stands, essentially unaltered in external appearance, in the southern part of the city. Perhaps, in the last analysis, the sentiment of the city was actually more Confederate

than Border-Line, and the Confederate Soldiers' Home, at Pikesville, now occupied by a fast dwindling number of inhabitants, is a point of interest. Within easy reach of Baltimore are the battlefields of Antietam and Gettysburg, while the Shenandoah Valley, replete with Civil War history, is a place of pilgrimage for hundreds of Baltimoreans annually in apple-blossom time.

Redwood Street, formerly German Street, one block south of Baltimore's central thoroughfare, bears the name of the first American soldier killed in the World War—a Baltimorean. The War Memorial, just across from the City Hall, is of interest for the beauty of its own construction as well as for the records of Baltimoreans and Marylanders in the struggle only recently ended.

But this is only a portion of Baltimore's historical aspects. Industrially and commercially, the city has seen many interesting developments. From its very foundation, Baltimore gave promise as a port of great advantages. Behind it notably in Frederick County, lies one of the richest agricultural sec-

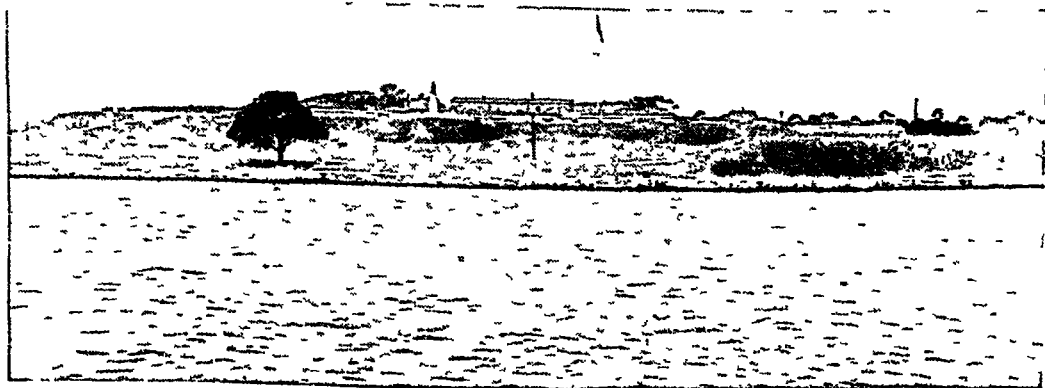


FIG 3 Fort McHenry—Baltimore, the birthplace of the Star Spangled Banner, our national anthem



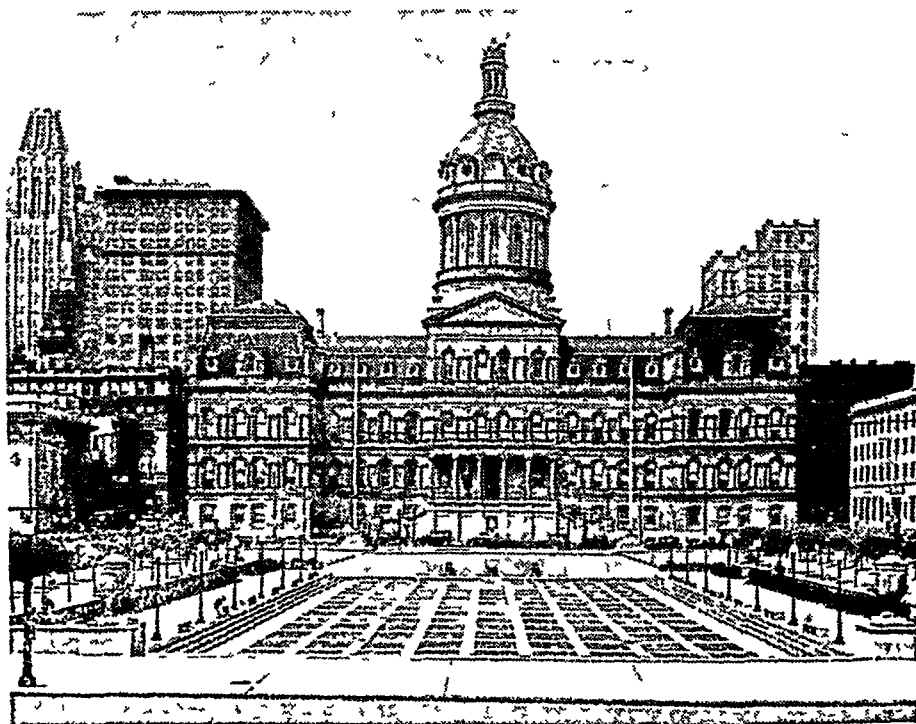


FIG 4 Civic Center—looking west from War Memorial across Memorial Plaza to City Hall in background

tions of the country Through the city, outward-bound, have passed throughout the years, the products of this rich hinterland, while inward-bound have passed the countless tons of imports necessary to the development of the South and West Here were built the swift, strong Clipper ships which, in numbers almost legion, outsailed all

other craft of their day and brought to port thousands of tons of coffee, sugar, molasses and choice West Indian tobacco—not to mention innumerable hogsheads of Jamaica rum

The list of "firsts" for Baltimore is a lengthy one To enumerate all its items would appear egotistical. Nevertheless, some of them can be given



with quite pardonable pride Here, in 1828, was established the Baltimore and Ohio Railroad, the first railroad in the country to initiate and continue a commercial service Mt Clare, the first railroad station in America, still stands on West Pratt Street, within walking distance of the University of Maryland School of Medicine It now serves as the construction and repair shops of the Baltimore and Ohio From it ran the "Old Main Line," the road's first stretch of track, which followed the shore of the Patapsco to Ellicott City, and subsequently to Frederick and the West From this station, in 1844, was sent to Washington, D C, the first Morse telegraphic communication in the United States

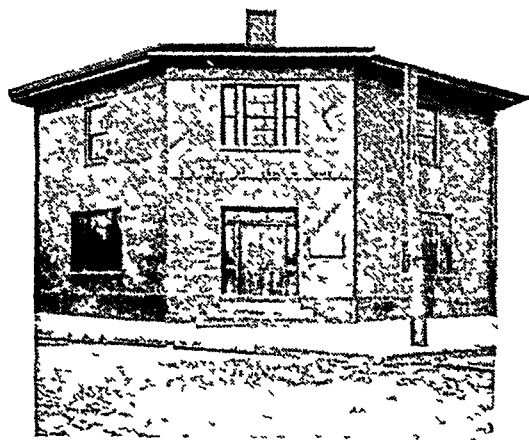


FIG 6 Mount Clare—first railroad depot in America

Baltimore was the city in which Meigenthaler brought the linotype to a working status From his first commercially practical machine, made in 1890, have sprung the vast developments in modern printing which now make possible such publications as this

Gas, for illuminating purposes was first made here in 1816, and we are

told on the authority of Cordell that Baltimore was the second city in the world—London being the first—to use this gas for the lighting of public highways Charles Varle, an engineer who writes of Baltimore in 1833, naively comments on the efforts of the Baltimore Gas Works to boost the sale of the resultant coke As for the coal tar, likewise resultant, he informs us that it offered an excellent preservative for ship timbers This was before the days of the modern steel industry and those wonderful chemical advances which now give us over 5,000 dyes from coal tar, a host of artificial perfumes and numerous drugs and medicines Within view of the City Hall stands a greatly treasured memento of Baltimore's industrial history This is the Shot Tower, said to be the only remaining structure of its kind in the world, a relic of the days before the du Ponts and the Krupps, when gravity was relied upon to mould the leaden balls

Baltimore to-day is a city of 805,753 inhabitants It contains about half the population of the State of Maryland Of these inhabitants, some 62% are shown by Federal Census Statistics to live in houses owned by themselves or their families, and the long rows of two-story dwellings, each with its white marble steps, have often elicited comments from visitors In population, Baltimore is eight among the cities of the country The growth of the city has been steady and substantial It has never enjoyed a boom or a mushroom growth Nevertheless to-day it ranks industrially as the seventh city in the country its annual output exceeding \$700,000,000 As a

port, it is third in the Nation's foreign trade tonnage. It is second only to New York as an Atlantic Coast port, and ranks *first* in intercoastal trade westward via the Panama Canal. Its wholesale trade is annually \$470,000,000, and its retail, \$360,000,000. In the last two years, it has given promise of becoming the aircraft manufacturing centre of the Eastern portion of the United States. The city lies on three passenger air routes and has a municipally-owned air-port which, when completed, will cover 1,000 acres.

Because of its geographical location, Baltimore is closer to the productive centres of the West—likewise closer

to the centre of population of the United States—than any other Atlantic port. Consequently, it enjoys a lower freight rate differential than New York, Philadelphia and Boston. Through Baltimore are routed exports from 38 States and Canada, and imports from 33 States and Canada. Three railroad trunk lines, the Baltimore and Ohio, the Pennsylvania and the Western Maryland, connect the piers of the city with all parts of the interior.

Baltimore's industries to-day are highly diversified. Some of its manufacturing plants are the largest of their kind in the country—even in the world.



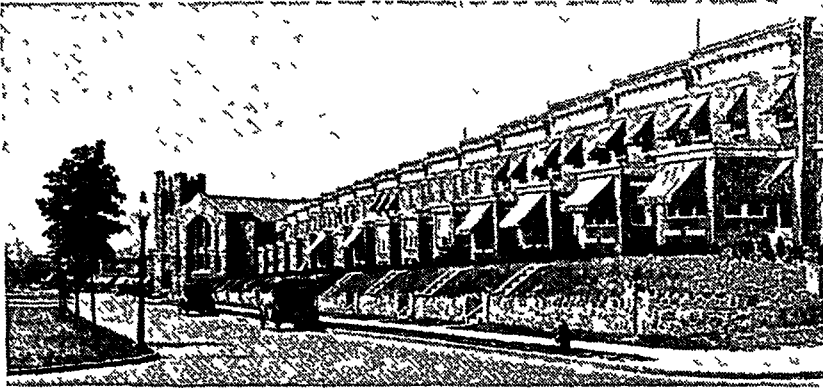


FIG 8 Row 2-story houses One family residences typical of Baltimore

These include the Baltimore Copper Smelting and Rolling Company, the Davison Chemical Company and McCormick and Company, The Sparrows Point Branch of the Bethlehem Steel Company and the American Sugar Refining Company are largest plants of their kind located on tidewater. A large part of the industrial alcohol used on the Atlantic Seaboard is made here,

and here are carried on most of the oil cracking processes that result in the gasoline used in this same section.

By virtue of its proximity to the Chesapeake Bay, an inland sea with fifty tributary rivers, Baltimore plays a prominent part in the fishing industry. Annually 2,500,000 bushels of oysters are taken from this bay, and in the distribution of this one form of



FIG 9 Roland Park Homes—part of the Roland Park Guilford-Homeland Development, one of the country's most beautiful suburbs

sea-food, both in its raw and canned states, Baltimore leads the country. Something to the same effect may be said of the blue crab, which, in normal seasons, is so plentiful that it can be scooped in nets from the bay's surface. The city's thriving canning industry is fed also by the surrounding agricultural region, for most of the tinned tomatoes used in the United States are put up here. In fact, both sea and land produce such a variety and abundance of good things to eat—among them the famous Maryland terrapin—that Oliver Wendell Holmes once called Baltimore the gastronomic centre of the universe.

In pursuing commercial success, Baltimore has not neglected intellectual development. To-day it is indisputably one of the medical centres of the world. It presents unusual facilities for the care of the sick, for research into the cause and cure of disease, and for the instruction of medical students. Almost indissolubly linked with

the name of Baltimore are the names of William H. Welch, Sir William Osler, Louis McLane Tiffany and John J. Abel, who in themselves have been termed epitomes of modern medicine. The city has two outstanding medical schools and more than 20 hospitals.

The fifth medical school to be established in the United States was founded here in 1807, under the name of the College of Medicine of Maryland. This institution, now the University of Maryland School of Medicine, has enjoyed an unbroken history of usefulness since its inception, supplying continuously most of the physicians of the State. Its central building, at Lombard and Greene Streets, which follows in general the external lines of the Pantheon at Rome, is the oldest building in the United States devoted to medical teaching. Here, for the first time in medical education, dissection was made a compulsory part of the curriculum, here, for the first time

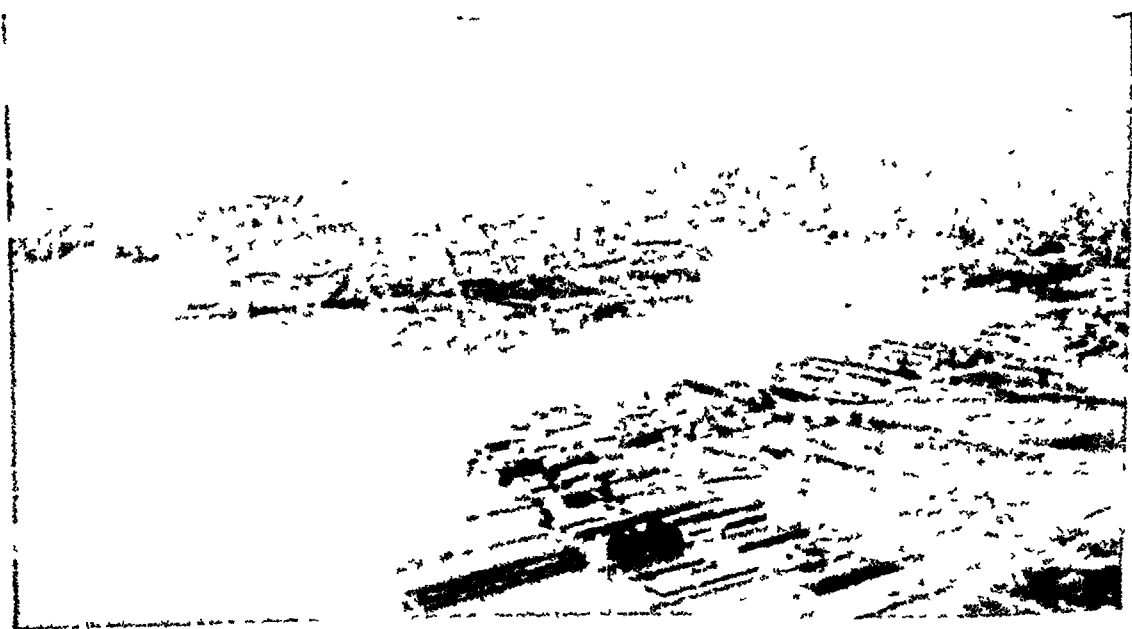


FIG. 20. BALTIMORE, Md.

in America, senior students were required to spend a portion of the year in residence in the hospital

The School of Dentistry and the School of Pharmacy, both branches of the University of Maryland, date respectively from 1840 and 1841. The former was the first institution in the world to be devoted exclusively to dental surgery.

In 1876, the Johns Hopkins University and the Johns Hopkins Hospital were founded through the generosity of a Baltimore merchant, whose

name these institutions now memorialize. Blazing a new trail, and introducing into the United States what now is termed "graduate learning," the University, through the men it assembled at its start—among them Gilman, Remsen, Sylvester, Martin, Rowland—has given a tremendous impetus to American letters, science and education. At Homewood, on the upper stretches of North Charles Street, are the University's collegiate and graduate departments of the arts and sciences. Some three miles distant, in

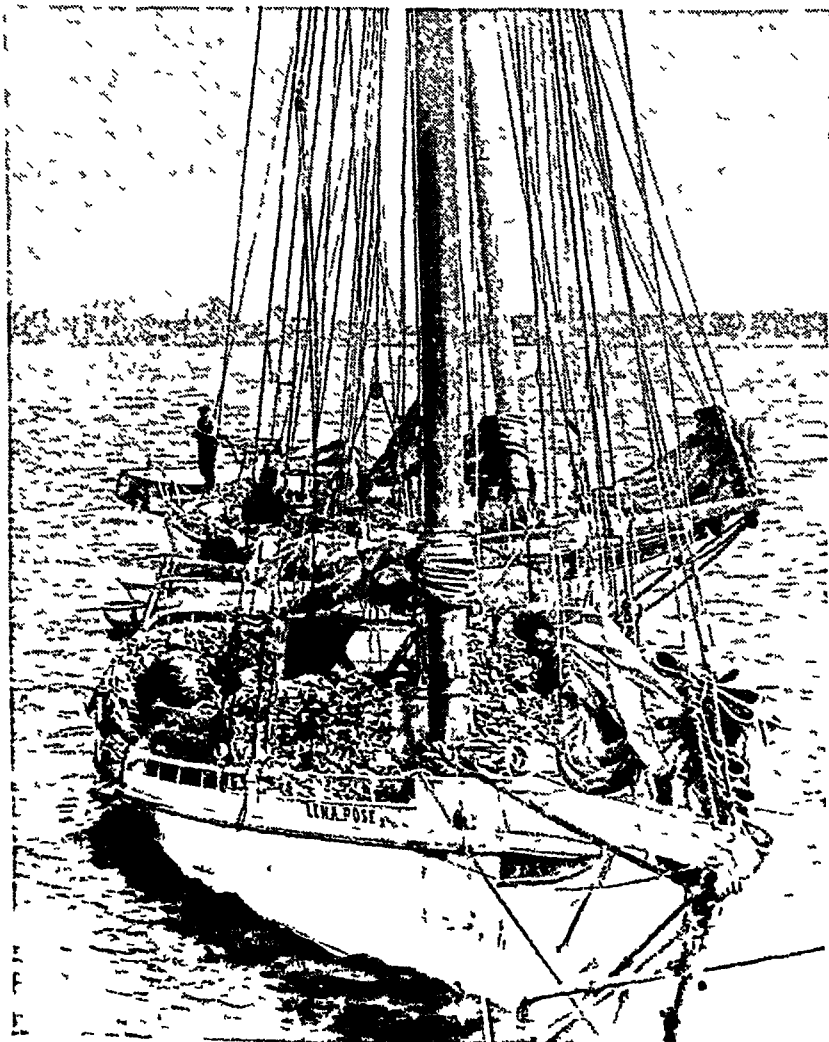


FIG. 11. Part of Chesapeake Bay oyster fleet.

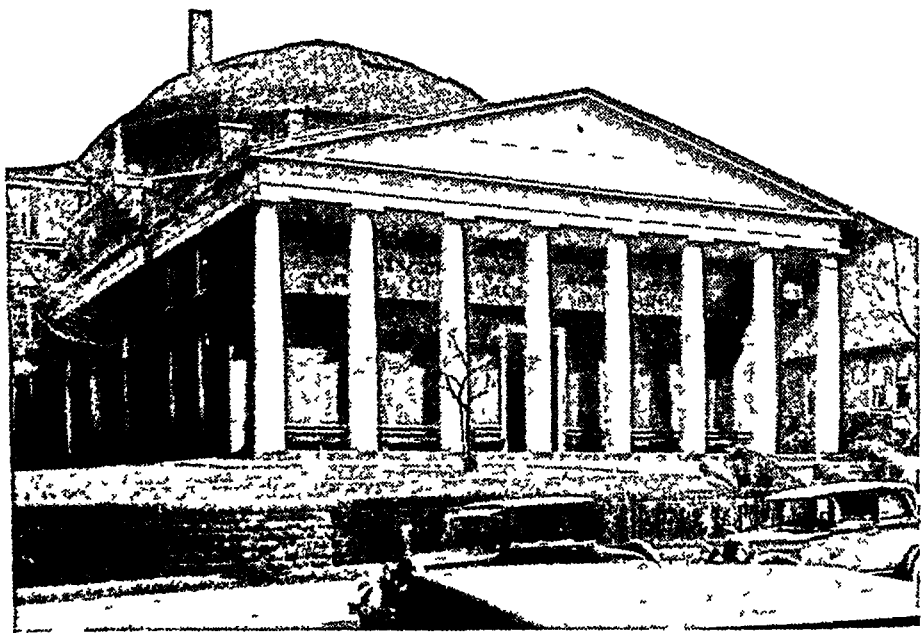


FIG 12 University of Maryland

close proximity to the Hospital, are the School of Medicine (opened 1893) and the School of Public Health and Hygiene (opened 1918)

Instruction in music is provided by the Peabody Conservatory, that in the

plastic and graphic arts, by the Maryland Institute of Art Just across the street from the Conservatory is the Walters Art Gallery, containing one of the finest private collections in the country Both the Gallery and the

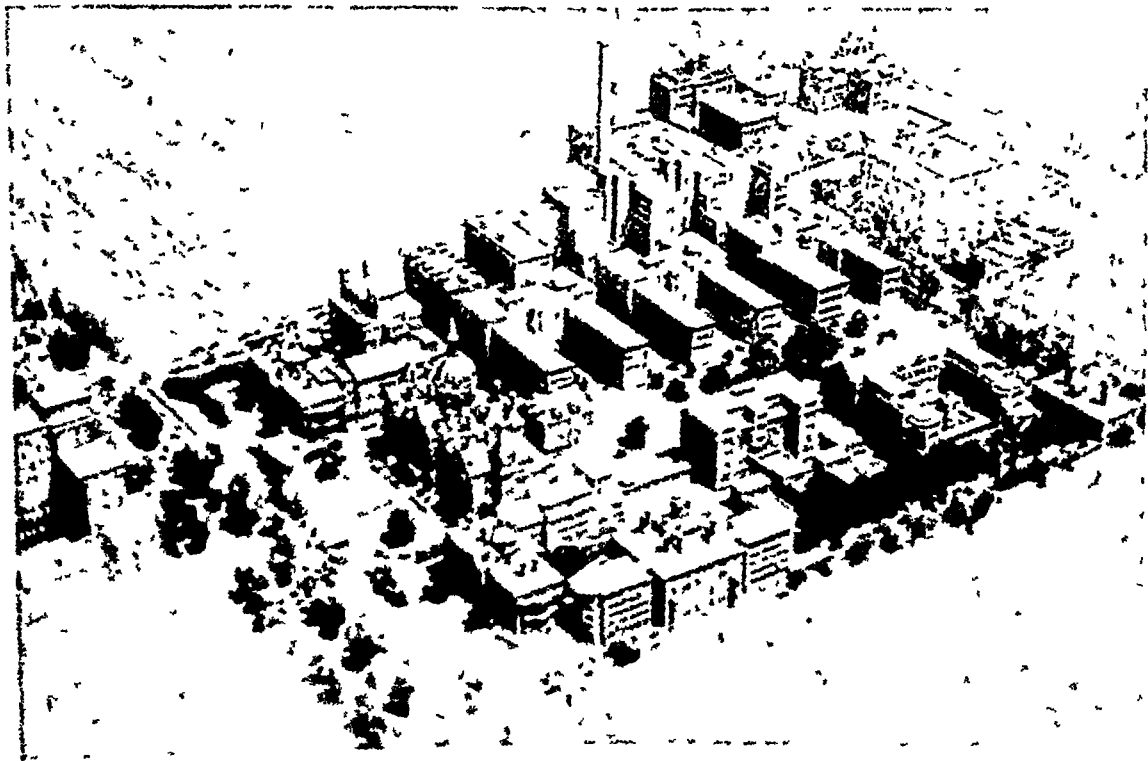


FIG 13 JOHNS HOPKINS HOSPITAL

Conservatory form a part of Baltimore's famous Mt Vernon Square, which, in addition to its own lines and its imposing buildings, is interesting for the local and National history memorialized in the monuments that adorn it. In this square, moreover, may be seen some of Barye's best bronzes.

In addition to the institutions mentioned above, Baltimore contains Goucher College for Women, Loyola College, Notre Dame Academy, St Mary's Seminary, and Morgan College (colored). Its library facilities are excellent. The Enoch Pratt Free Library (established 1882) has approximately 600,000 books available for circulation in the city. For the student and scholar, these are augmented by the reference library of the Peabody Conservatory (253,000 books), the library of the Medical and Chirurgical Faculty (38,000 books), in addition to the libraries of the University of Maryland and the Johns Hopkins University. The William H. Welch Medical Library constructed on an appro-

priation of \$750,000, from the General Education Board, was opened in 1929. This building is equipped especially for the collection, housing and utilization of medical works, as well as for the development of an Institute of the History of Medicine. Washington is so near, and the inter-library loan system so well managed that Baltimore scholars enjoy practically all the many advantages of the Library of Congress.

In literature, Baltimore has enjoyed an ample share. Much of the life of Edgar Allen Poe is connected with the city. Here he wrote "The Raven." The poet is buried in old Westminster Church yard, at Fayette and Greene Streets, and a statue has been erected to his memory at Wyman Park, near the Johns Hopkins University. Sidney Lanier, poet, musician and literary critic, was connected with Hopkins in its early days. Here to-day lives Lizette Woodworth Reese, author of the sonnet "Tears," and numerous other poems that have won her well merited renown.

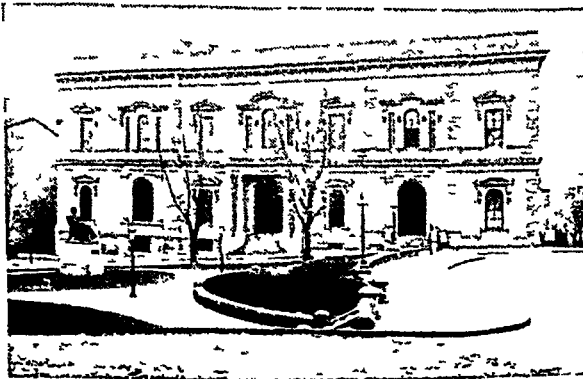


FIG. 14 Peabody Institute established in 1868 by George Peabody





FIG 15 Grave of Edgar Allan Poe Westminster Churchyard—Baltimore

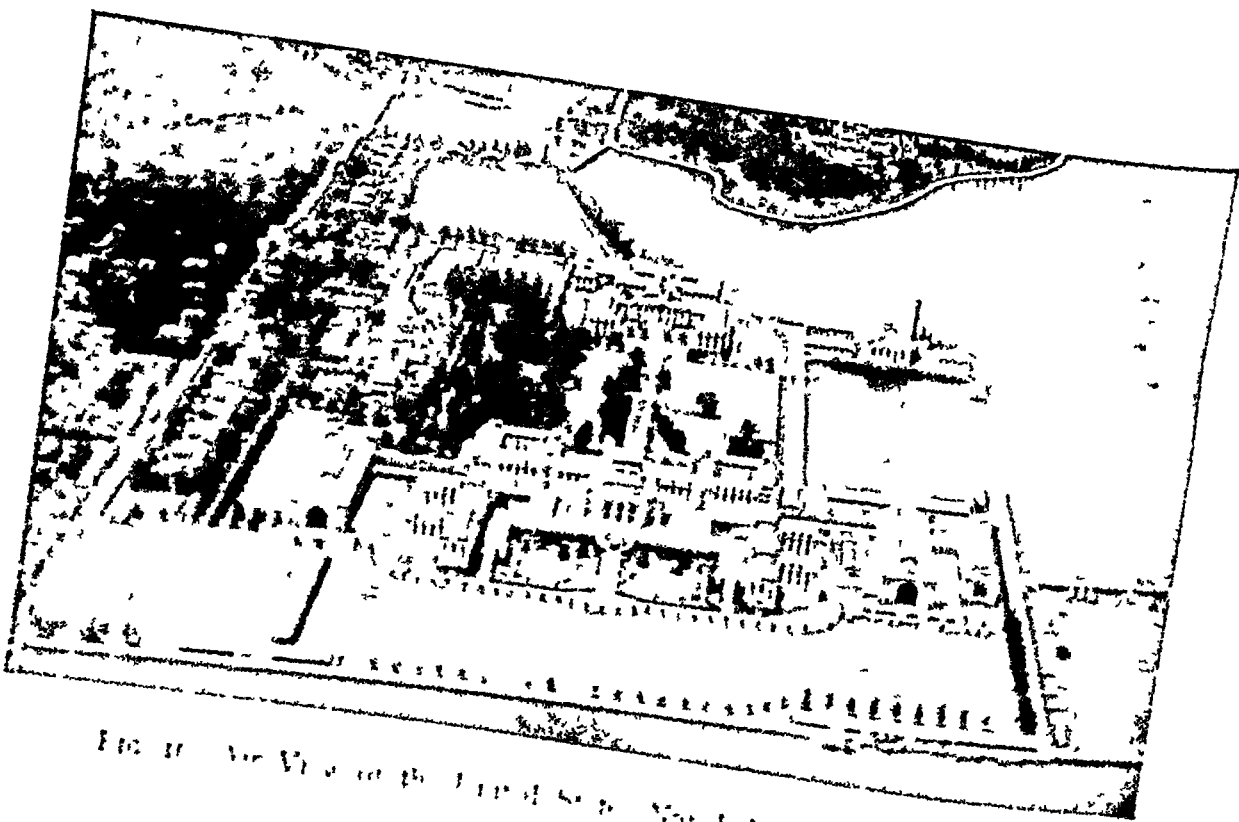


FIG 16 Air View of Baltimore, Maryland

To continue about Baltimore would fill many pages, for a city which for over two hundred years has grown steadily in physical assets, giving heed all the while to the things of the soul—as Baltimore has done—will have much to say for itself. The truth of this will be seen most forcefully when one stops to consider how peculiarly vital in the experiences of the world have been the years from 1729 to 1931. But Baltimore is not all of Maryland. Distant only a pleasant morning's or afternoon's drive along good roads and through inspiring country, are Annapolis and Frederick. A well informed writer has said that were George Washington to come back to life, he would still feel perfectly at home in Annapolis, so lightly has the hand of

change rested upon it. Its outstanding points of interest are the beautiful old State House, St. Johns College and the United States Naval Academy. At the Academy rest the remains of John Paul Jones, the country's first admiral. In Revolutionary history, Annapolis is famous as the place of the burning of the "Peggy Stewart" in defiance of the tea tax. At Frederick, another wealth of historical associations lies in store, centering about the gallant stand of Barbara Fritchie.

Moreover, a wide boulevard, accommodating four automobiles at once, conducts one by an easy hour's drive to Washington, the Nation's Capital. Few, indeed, of those visitors from afar to Baltimore can resist this drive

# College News Notes

## THE FORTHCOMING CLINICAL SESSION IN BALTIMORE

The Fifteenth Annual Clinical Session of the American College of Physicians will convene in the City of Baltimore during the week of March 23, 1931. The privilege of meeting in this city was made possible through the cordial invitation of the Johns Hopkins University School of Medicine, the University of Maryland School of Medicine, the Medical and Chirurgical Faculty of the State of Maryland, the Baltimore City Medical Society, and the further cooperative interest manifested by the various Baltimore hospitals and civic societies. It is to be hoped that this meeting will at least equal in excellence those which have been produced in recent years in other cities, and it is the belief that all who will attend this meeting will find ample in the way of clinical, laboratory, research and historical interest, well to repay them for the time spent in making the journey.

Local conditions, as well as medical and hospital facilities, greatly affect and alter the construction of programs, and at this writing the actual titles of papers and clinics to be presented, by whom, when and where, are far from being in a completed and final state. Moreover, it is possible that for reasons, both of economy and others, the former precedent of issuing a preliminary program may not be lived up to, though this

At the risk of repetition, the following points with reference to the meeting will bear repetition.

(1) *Time and Place*: March 23-27, 1931, in Baltimore, Maryland.

(2) *Hotel Headquarters* will be at the Lord Baltimore Hotel, and it is important at this point to emphasize the wisdom of making early hotel reservations, whether they be at Hotel Headquarters or at some other of the hotels listed at the end of this article.

(3) *General Headquarters*, at which the registration of members, commercial exhibits and all General Sessions will be held, will be the Alcazar, situated at the corner of Cathedral and Madison Streets Baltimore, unfortunately, is not yet the proud possessor of a convention hall or auditorium at all adequate to its needs, nor comparable to the buildings of this sort found in cities of smaller population. Nonetheless, it is felt that the Alcazar will meet all of the requirements of the College meetings, and all of the meetings, exhibits, registration offices, etc., are located on the same floor, and in easy access to one another.

The skeleton outline of the entire Clinical Week is given in the diagram below, and certain points require particular emphasis.

(1) Those who are planning to attend the Clinical Session should arrange to reach Baltimore before 6 P. M. on March 22.

FIFTIETH ANNUAL CLINICAL SESSION  
BALTIMORE, MARYLAND, 1931

Time	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday
A M	March 23	March 24	March 25	March 26	March 27	March 28
9 00 to 12 30	Morning free Registra- tion Exhibits, etc	3rd <i>General Session</i>	5th <i>General Session</i>	6th <i>General Session</i> General Business Meeting	7th <i>General Session</i>	Entire Day in Washington, D C Clinics, Inspection Tours, etc Under Auspices of Medical Departments of Army, Navy, U S Public Health Service, and Georgetown University  — Full details not yet ready
12 30 to 2 00 P M	Lunch					
2 00 to 5 00 P M	1st <i>General Session</i>	1st <i>Clinical Session</i>	2nd <i>Clinical Session</i>	3rd <i>Clinical Session</i>	4th <i>Clinical Session</i>	
5 00 to 8 00	Dinner					
8 15 to 10 30	2nd <i>General Session</i>	4th <i>General Session</i>	Convoca- tion and Reception to New Members	Annual Banquet	FREE	

General Session, to be held Monday afternoon, is not only desirable but is a courteous acknowledgment to the hosts of the entire meeting. It is the sincere hope of the Program Committee that the hall will be filled when the meeting is called to order sharply at 2 o'clock on the date above mentioned.

(2) It is to be noted that the Convocation this year will be held earlier than has been the custom in the past. Further reference to this will be made in a subsequent paragraph.

(3) It is to be noted that the Clinical Sessions of the meeting will occur in the afternoon, rather than in the morning. This plan has been adopted particularly for the reason that it interferes much less with the teaching of medical students at the Johns Hopkins Medical School and University of Maryland. It will be remembered that this same plan was followed at the meeting in New Orleans, with apparently just as great

success as when the sessions were reversed.

(4) The Annual Banquet will be held on Thursday evening, March 26, presumably at the Lord Baltimore Hotel, and to this, as in times past, ladies are cordially invited.

(5) After the Clinical Sessions have been finished on Friday, March 27, there will be held a Post-Clinical Session Day in Washington, D C, for all those who care to attend what promises to be an extremely interesting and valuable meeting there.

#### GENERAL SESSIONS

At the last meeting of the Board of Regents that was held during the Minneapolis Session, it was decided that the President of the College would be held responsible for the programs of the General Sessions, of which there are seven in all. Following the Minneapolis meeting, the Executive Secretary of the College, Mr. Loveland, sent out a questionnaire to all of the Fellows and

Associates of the College, asking for ideas and suggestions for the improvement or alteration of subsequent programs. Many replies of value were received, and the answers analyzed, and an attempt has been made by your President to embody as many of the suggestions submitted as possible in the construction of the General Sessions Program. The main changes that he has attempted to make may be briefly summarized, as follows:

(1) The number of papers in the General Sessions will be fewer than has hitherto been the case—probably never in excess of eight papers, of a maximum of twenty minutes each, in any of the morning sessions, which will run from 9 until 12:30.

(2) The morning sessions will be broken mid-way by an intermission of thirty minutes, which will provide not merely a period of relaxation for the audience but will afford an opportunity for every member of the College to make a careful inspection of all of the exhibits. The importance of this cannot be over-emphasized, for it should be pointed out that the exhibits go a long way toward defraying the expenses of the Annual Clinical Session itself; and, moreover, the exhibits offered are invariably worthwhile, from the standpoint of the internist. It has been none too easy a task to assemble as many exhibits as Mr. Loveland has been successful in securing, partly for the reason that exhibitors are aware of the fact that the members of the College will probably be away from the exhibition hall at least half of each day of the Session.

anything, over-handled—as, for instance, articles on tuberculosis and hypertension; and, second, the fact that the same individual had presented papers on two and sometimes on three succeeding programs. It was thought wise, therefore, to endeavor to provide a series of articles which dealt as much as possible with new subjects; and furthermore, it was decided that an individual who had appeared twice within the last preceding three years would not be invited to present a paper at this particular Session. This plan seemed manifestly fair to all to whom the problem was presented.

In the attempt to secure the greatest possible number of submitted titles, the following general method has been employed.

(1) Personal letters have been sent to a great many individuals, whether members of the College or not, throughout the entire United States and Canada.

(2) A letter was sent to the Governor of every state and territory, asking that he in turn submit the names of all Fellows, or of individuals not members of the College, in his State, who, in his opinion, might have material interesting and worthy of presentation before the College; and to every such person a letter was subsequently sent, requesting that the individual in question submit a title or titles of papers which he might care to present. It was clearly pointed out at the time that all of these letters were sent, that the mere submission of a title or titles in no way obligated the Program Committee to accept them.

be the result of personal ideas and opinions, by any means. The hope is expressed that those who have shown their willingness to read papers will clearly understand, and entertain no hard feelings, if it is found wise to reject their proposed addresses.

The number of possible symposia of great interest is very large. Under consideration at the present time are symposia on blood diseases, oxygen therapy, diseases of the liver, recent advances in endocrinology with particular reference to the newer work on supra-renal extracts, myocarditis, and several others which it is not necessary to mention. The greatest difficulty is to know which of the many equally valuable and interesting ones to accept, obviously, the individual tastes of everyone cannot be met.

#### CLINICAL SESSIONS

To Doctor Maurice C. Pincoffs, Professor of Medicine at the University of Maryland, was delegated the task of arranging for all of the Clinical Sessions. Baltimore has but two medical institutions of learning, namely, Johns Hopkins and the University of Maryland itself. Scattered throughout the city are many modern and excellently run hospitals, in which, however, little if any active teaching is done, at least in conjunction with either of the two Medical Schools. Obviously, the focus of greatest attraction will be the various departments at the Johns Hopkins Hospital and Medical School, and it should be stated at this time that the Heads of all of the Departments of this institution have expressed and are showing an enthusiastic interest in the construction of a program which will open all of the facilities of this enormous plant to the visiting members of the College. The active organization and work, in so far as it concerns the Johns Hopkins Hospital, is under the able administration of Doctor Alan M. Chesney, Dean of the Medical School, and a committee appointed by him. A similar committee, acting under Doctor Pincoffs, will supervise the Clinical Programs to be held at the University of Maryland and its affiliated Hospital. In addition, clinics, ward walks, laboratory demonstrations and the like will be held in many of the non-teach-

ing hospitals of the city, such as the Union Memorial Hospital, Saint Agnes Hospital, at which Doctor Joseph C. Bloodgood does so much of his work, the Municipal Hospitals, and several of the more private institutions, such as the Howard A. Kelly Hospital, noted particularly for its radium activities, and the Sheppard and Enoch Pratt Hospital, which is one of the most modern dealing with psychiatric problems. This does not by any means exhaust the list.

It has been customary in former meetings to have a certain number of clinics given by distinguished out-of-town clinicians, either Fellows of the College or invited guests, and this custom will be followed again this year, in all likelihood.

It should be further noted that the program, in so far as it concerns Johns Hopkins, will include both the pre-clinical as well as the clinical facilities. The work of the Harriet Lane Home in Pediatrics, the Wilmer Institute for Diseases of the Eye, the Phipps Psychiatric Institute, headed by Doctor Adolf Meyer, and, moreover, the surgical facilities of the Hospital are already being marshalled for the presentation of such border-line problems as are of equal interest to surgeons and internists alike. The Johns Hopkins School of Hygiene and Public Health, with Doctor William H. Howell as its Director, will provide its own program of subjects and demonstrations of interest particularly to Public Health workers and those deeply interested in all lines of Preventive Medicine. Last, but by no means least, the new William H. Welch Department of Medical History will offer a program unique in the annals of the College. As above stated, final details as to topics, clinicians giving them, etc., have not yet been worked out in any of the hospitals, but from the above it can readily enough be seen that plenty can and will be provided to suit the tastes and interests of everyone.

#### CONVOCATION

The Annual Convocation of the College, for the induction of new members, as Masters or Fellows, will be held on Wednesday evening, March 25, at a time and place subsequently to be announced. It is felt that

this is, or at least should be, the most formal gathering which the College holds during its Clinical Session; and it is, therefore, earnestly urged that all members and those to be inducted will appear in evening dress on this occasion, at which time the annual Presidential Address is to be given. Following the Convocation, it is hoped that an appropriate reception to the new members can be held, affording them a chance to meet and know not only the Officers of the College, but also to mingle with those who have been members for varying periods of time. Just how this can best be worked out is still under consideration, but again, it is hoped that this meeting will be fully attended.

#### LADIES ENTERTAINMENT COMMITTEE

It is hoped and presumed that the Baltimore Session will be graced by the presence of many of the wives of the attending members of the College. Baltimore has long been famed for its hospitality, and it is an assured fact that an interested and hospitable Ladies Entertainment Committee will see to it that all visiting ladies are interestingly occupied during their stay in Baltimore. Like many other committees, the final plans have not yet been drafted; but no doubt need be entertained as to their fitness and pleasure.

#### POST-SESSION WASHINGTON DAY

It was felt that a great many of the members, particularly those coming from some distance, would not wish to return without paying a visit to the National Capital, particularly if some of the unusual medical facilities of that city could be assembled for their interest and instruction. With this in mind, the matter was taken up with Doctor William Gerry Morgan, President of the American Medical Association and Governor of the American College of Physicians for the District, and through his influence a luncheon was recently held in Washington, at which a number of men of national importance were present, including Surgeon General Ireland, of the Army, Doctor Hugh S. Cummings, Surgeon General of the United States Public Health Service, Doctor C. M. Griffith, Medical Director of the United States Veterans Bureau, Doctor W. A. White, Superintendent of Saint Elizabeth's Hospital; a representative from the United States Naval Medical School, and others, including the President of the Medical Society of the District of Columbia. These men enthusiastically offered their heartiest cooperation in the preparation of a memorable Washington Day, and the number of interesting possibilities was so great that it seemed well, almost, to change the entire route from Baltimore to Washington itself. The facilities of Saint Elizabeth's Hospital and its unusual opportunities of instruction, the Library of the Surgeon General, Army Medical Center, Army Medical School, Walter Reed Hospital, the Smithsonian Institution, the Institute of Pathology, and all will be available in a plan

which yet remains to be worked out, and this, in turn, will depend largely upon the number of members who express their desire and intention to attend the Washington Meeting

Such, in schematic form, is the general lay-out for the forthcoming meeting. It is

hoped that the lack of specific details will at this time incite rather than dampen further interest in the meeting itself. At least it can be truthfully stated that Baltimore's welcome will be a wholehearted and unstinting one, and it is believed that all who come will leave repaid.

#### LIST OF BALTIMORE HOTELS

The LORD BALTIMORE HOTEL will be the headquarters hotel for Officers, Regents and Governors, and so far as facilities permit, will accommodate other members and guests of the College. Reservations that the LORD BALTIMORE HOTEL cannot fill, will be referred immediately to some other hotel conveniently located. Those who plan to attend the Baltimore Clinical Session should apply directly for reservations to the hotel of their choice.  
(All Prices are for Rates per Day, European Plan)

##### LORD BALTIMORE, Baltimore and Hanover (Headquarters)

Single room with bath	\$3 50 to \$ 6 50
Double room with bath	5 50 to 10 00

##### ALTAMONT, Eutaw Place and Lanvale St

Single room without bath	2 50
Single room with bath	3 00 to 3 50
Double room without bath	4 00
Double room with bath	5 00 to 6 00

##### ARUNDEL, Charles St and Mt Royal

Single room without bath	2 00 to 2 50
Single room with bath	2 50 to 3 50
Double room without bath	3 00 to 3 50
Double room with bath	5 00 to 6 00

##### BELVEDERE, Charles and Chase Sts

Single room with bath	5 00 to 6 00
Double room with bath	7 00 to 12 00

##### EMERSON, Baltimore and Calvert Sts

Single room without bath	2 50
Single room with bath	3 00 to
Double room without bath	4 00
Double room with bath	4 50 to

##### KERNAN, Franklin and Howard Sts

Single room without bath	2 00 to 3 00
Single room with bath	2 50 to 3 50
Double room without bath	3 00 to 4 00
Double room with bath	4 00 to 6 00

##### MT ROYAL, Mt Royal Ave and Calvert

Single room without bath	2 00 to 2 50
Single room with bath	3 00 to 3 50
Double room without bath	4 00 to 4 50
Double room with bath	5 00 to 6 00

##### NEW HOWARD, Howard St and Baltimore

Single room without bath	2 50 to 3 00
Single room with bath	3 00 to 3 50
Double room without bath	4 00 to 5 00
Double room with bath	5 00 to 6 00





## Reprints

- "'Arbitrary Period of Disability' As a Mode of Settlement in Compensation Claims"
- "Auricular Flutter Following Direct Injury to the Chest"
- The Influence of Venous Filling on the Heart"
- "Aneurysm of the Left Ventricle"
- "Four Cases of Multiple Myeloma"
- "A Case of Subacute Infective Endocarditis with Mycotic Aneurysm and Meningeal Symptoms"
- "Serum Treatment of Postinfluenzal Bronchopneumonia"
- "Health Supervision of Employees in Financial Organizations"
- "Principles of Conducting a Cardiac Clinic"
- "Contraceptive Advice and the Medical Profession"
- "A Municipal Birth Control Clinic"
- "Elevators for Children's Schools"
- "The Human Dying Heart" (with Israel Goldstein)
- "A New Vascular Sign of Death"
- "Quinidine in Treatment of Cardiac Decompensation" (with Sidney B Wilensky)
- "The Position of the Arm in Blood Pressure Measurements"
- "A Method for Recording Continuous Blood Pressure"
- "Present Status of Curability of Bronchial Asthma"
- "The Classification of Asthma"
- "Cardiac Asthma"
- "Angina Pectoris"
- "Etiologic Factors in Angina Pectoris"
- "Prodromal Symptoms in Angina Pectoris"
- "Cardiovascular Lesions Following Injury to the Chest" (with Samuel Kahn)
- "The Medical Critic and Guide — Journal"

Dr William D Reid (Fellow) Boston, Reprint

Dr Blanton P Seward (Associate), Roanoke, Va

## Reprints

- "Factors in the Prognosis of Arterial Hypertension"
- "The Rational Use of Digitalis"
- "Coronary Occlusion, with Report of a Case"
- "A Clinical Study of Visceroptosis"
- "The Necessity for a Careful Pre-operative Medical Examination of Surgical Patients and the Recognition of Postoperative Circulatory Disturbances"
- Dr Virgil E Simpson (Fellow), Louisville, Ky

## Reprints

- "Gall Bladder Disease"
- "Food Content with Relation to Density and Composition of Stone in Upper Urinary Tract" (With Owsley Grant)
- Dr Walter M Simpson (Fellow), Dayton, Ohio

## Reprint

- "Undulant Fever (Brucellosis)"
- Dr Max H Weinberg (Associate), Pittsburgh, Pa

## Reprints

- "Epidemic (Lethargic) Encephalitis"
- "Unusual Case of Cerebrospinal 'Giant-Cocci' Meningitis"
- "Spinal Cord Tumors"

Dr Harold S Hatch (Fellow), Indianapolis, has been appointed as a member of the Board of Trustees of the State Sanatorium at Rockville, Ind

At the Annual Fall Conference of the Oklahoma City Clinical Society, held November 5-7, 1930, the following members of the College offered clinics or demonstrations as indicated below

Dr P M McNeill (Associate), "Bronchiectasis"

Dr C J Fishman (Fellow) 'Demonstration of Fundamental Neurological Signs'

Dr Ray M Balyeat (Fellow), 'Demonstration of Cases Illustrating Five Allergic Syndromes in Children'

Dr. Lea A. Ruby (Fellow), "Diabetes"  
 Dr. Wm. L. Lupton (Fellow); "Arthritis"  
 Dr. Arthur B. Chace (Fellow), "Cardiac Complications of Arthritis"  
 Dr. Arthur W. White (Fellow); "Gastric Ulcer"

Dr. Sydney A. Portis (Fellow), Chicago, and Dr. I. S. Frostler (Fellow), Chicago, are authors of "The Clinical Significance of Roentgenological Findings of the Non-Malignant Colon" and "A Milligramme Minute Dose Table for Superficial Therapy," respectively, in the December Issue of RADIOLOGY

At the third spring clinical conference of the Dallas Southern Clinical Society, to be held at Dallas, Texas, March 30 to April 3, 1931, the following Fellows of the College will contribute to the program.

Dr. Walter C. Alvarez (Fellow), Rochester, Minn. and Dr. James H. Means (Fellow), Boston, Mass.

At the Scientific Meeting of the Allegheny County Medical Society, on November 18, at Pittsburgh, Dr. Ernest W. Willetts (Fellow) gave a paper on "Agranulocytosis", Dr. Lester Hollander (Fellow) gave a paper on "Eczema from the Allergic Standpoint", and Dr. Max H. Weinberg (Associate) presented "A Case of Pneumococcus Type III Meningitis with Recovery, Treated with Potassium Permanganate"

Dr. Frank A. Evans (Fellow), Pittsburgh, Pa., is the author of "Pernicious Anemia," a book published by the Williams & Wilkins Co.

Dr. Oliver T. Osborne (Fellow), New Haven, Conn., is the author of an article entitled, "The Cost of Medical Care," which appeared in the Medical Journal and Record, November 5, 1930, page 426

Dr. Ellen C. Potter (Fellow), Director of Medicine, Department of Institutions and Agencies of New Jersey, addressed the

annual meeting of School Nurses of New Jersey on the subject of "The School Nurse and Mental Hygiene" at Atlantic City, November 11, and was guest speaker at the annual dinner of the State Conference of Social Work at Wilmington, Del. November 13, her subject being "Experiments in Democracy in the Field of Social Welfare"

Dr. Sinclair Luton (Fellow), St. Louis, Mo., gave an address on "Diagnosis of Chronic Heart Disease (with Clinical Demonstration, Lantern Slides and Moving Pictures of Heart Valves in Action)" before the Southwest Missouri Medical Society at Springfield, Mo. November 6. Dr. Luton also gave an address entitled "Danger Signals in Chronic Heart Disease," before the forty-eighth annual meeting of the Wabash Railway Surgical Society at St. Louis November 10

The name of Dr. Anthony A. Rutz (Fellow), Brooklyn, N. Y., should be omitted from the present Directory of the American College of Physicians due to his death on May 3, 1928, although not reported to the College until October 11

Dr. Albert S. Hyman (Fellow), Director of the Witkin Foundation for the Study and Prevention of Heart Disease, Beth David Hospital, New York City, presented a paper on October 28, 1930, upon "Coronary Occlusion Simulating the Acute Surgical Abdomen, Report of three Cases Operated Upon," before the Metropolitan Medical Society

On November 10, 1930, he presented a paper upon "Subacute Bacterial Endocarditis," before the Beth David Hospital Clinical Society

On November 17, 1930, he gave a demonstration upon the "Irregularities of the Fetal Heart—A Phonocardiographic Study of the Fetal Heart Sounds from the Fifth to Eighth Months of Pregnancy," before the Yorkville Medical Society

The November 17th meeting of the Yorkville Medical Association, New York City,

was a symposium upon Diseases of the Heart. The program was as follows:

Dr Joseph B Wolffe (Associate), Philadelphia, spoke on "The Hormone Vaso-dilators in the Treatment of Vascular Diseases with Special Reference to Angina Pectoris."

Dr Aaron E Parsonnet (Fellow), Newark, N J, spoke upon "Myocardosis, the Failing Heart of Middle Life."

Dr Albert S Hyman (Fellow), New York City, spoke on "Irregularities of the Fetal Heart, A Phonocardiographic Study of the Fetal Heart Sounds from the Fifth to Eighth Months of Pregnancy."

In the International Clinics (Philadelphia), September and December 1930 volumes, appeared a paper by Dr H I Goldstein (Associate), Camden, N J, on "Ossler's Disease", "Hypocalcemia with Hypothyroidism and Tendency to Bleeding" appeared in the Medical Journal of the Medical Society of New Jersey, and Dr Goldstein's paper on "Recent Advances in Treatment" appeared in American Medicine (New York City), July and August, 1930, Issues

Dr Eugene R Whitmore (Fellow), Washington, D C, with Dr Wallace M Yater, delivered a paper on "Carcinoma of the Liver" before the Medical Society of the District of Columbia on November 26. This paper was discussed by Dr Lester Neuman (Fellow), Washington, D C. Dr C B Conklin (Fellow), Washington, D C, is the Secretary of the Society.

Dr Fred C Oldenburg (Fellow), Cleveland, was elected Chief of the Medical Department of Charity Hospital, also Director of the Medical Dispensary. Both of these appointments were sanctioned by the Faculty of the School of Medicine of Western Reserve University. Dr Oldenburg continues as Secretary of the Staff of Charity Hospital.

Dr John P Sawyer (Fellow), Cleveland, was elected Chief of the Staff of Charity Hospital. The appointment was sanctioned

by the Faculty of the School of Medicine of Western Reserve University.

Dr Arthur R Elliott (Fellow) and Dr George H Coleman (Fellow), both of Chicago, are President of the Chicago Society of Internal Medicine and Secretary of the Institute of Medicine of Chicago, respectively.

Dr E Rodney Fiske (Fellow), New York City, Lecturer, Diseases of the Chest, New York Homeopathic Medical College and Flower Hospital, is the author of an article, "Basic Principles Underlying Homeopathic Prescribing in Cardiovascular Disease." The original paper was read before the Bureau of Homeopathy at the 86th annual convention of the American Institute of Homeopathy, Atlantic City, N J, June 18, 1930.

Dr Ray M Balyeat (Fellow), Oklahoma City, Lecturer on Allergic Diseases, University of Oklahoma School of Medicine, is the author of a book, "Allergic Diseases, Their Diagnosis and Treatment."

Dr Thomas Noxon Toomey (Fellow), St Louis, Mo, is the author of a book on Dermatology, "The Treatment of Skin Diseases in Detail."

On November 7, 1930, Dr Curran Pope (Associate), Louisville, delivered an address over the Radiophone of WHAS, the Courier Journal and Louisville Times. The address was delivered at the request of the Disabled Veterans of Kentucky. Dr Pope took as his subject, "For-Get-Me-Not Day."

On Armistice Day, November 11, 1930, Dr Curran Pope, speaking under the auspices of The National Security League of New York, delivered a Radiophone talk over the Radiophone of WLAP. The subject of Dr Pope's address was, "Armistice Day," dealing with the patriotic activities and the meaning of the day.

Dr Edward C Mason (Fellow) has removed from Springfield, Mo to become connected with the Medical Department of the University of Oklahoma and resides in Oklahoma City.

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Dr Benjamin Goldberg (Fellow), Medical Director of the City of Chicago Municipal Tuberculosis Sanatorium Organization, and Associate Professor of Medicine, University of Illinois, was the speaker at a joint meeting of the Jefferson County Medical Society and the Louisville Tuberculosis Association at Louisville, Ky., on Monday, December 1, 1930. His topic was "Tuberculosis Control and the General Practitioner."

Dr Goldberg also addressed a noon luncheon meeting of the Hospital Directors' Association at Louisville on the same day. At this time he spoke on "Clinic and Sanatorium Management of Tuberculosis."

Medical Department Research Board at the Bureau of Science, Manila, P. I., has been transferred to Washington, D. C., and is now in charge of the Bacteriological Department of the Army Medical School.

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Dr Carl V. Weller (Fellow), Ann Arbor, delivered a paper on "Primary Carcinoma of the Lung" before the Rochester Academy of Medicine, December 3rd.

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The Eleventh Annual Pasteur Lecture was delivered before the Chicago Institute of Medicine, November 11th, by Dr Aldred Scott Warthin (Master), on "Problems of Latent Syphilis."

## OBITUARY

On Sunday, November 23, 1930, John Welsh Boyce (Fellow) died in Southside Hospital, Pittsburgh, following a gall-bladder operation

Dr Boyce was born in Sligo, Pa., in 1871 and graduated from the University of Pittsburgh School of Medicine in 1892. During his medical career he served on the staffs of the Western Pennsylvania and Southside Hospitals, was consulting physician to the Eye and Ear Hospital, and visiting physician to the City Hospital at Mayview where he gave freely of his time and talents. During the world war he served in the medical department at Camp Jackson with the rank of Major.

For more than thirty years Dr Boyce served officially in one office or another in the Allegheny County Medical Society, and since 1921 was Associate Editor of its official organ, the Pittsburgh Medical Bulletin.

He is survived by his widow, Mrs Tracy Carter Boyce.

Dr Boyce, until his health began to fail, was a regular attendant upon medical meetings, and being endowed with a keen intellect, unusual facility in expression and a forceful individuality, his discussions upon his chosen field of practice, diseases of the chest, were never lacking in interest and benefit to those who were privileged to hear them.

An interesting sidelight upon Dr Boyce's versatility is shown by the fact that early in his medical career he became interested in some phases of legal procedure, studied law, passed the state examinations and was admitted to the Allegheny County Bar.

Since 1922 Dr Boyce has been a Fellow of the American College of Physicians and in his death the College sustains a very real loss.

—Furnished by E. Bosworth McCready, M.D., F.A.C.P., Governor for Western Pennsylvania.

## PRESTON MANASSEH HICKEY

Dr Preston Manasseh Hickey, Professor of Roentgenology at the University of Michigan, died at his home in Ann Arbor, October 30th, 1930, from cardio-vascular-renal disease. Dr Hickey was born in Ypsilanti, Michigan, December 3rd, 1865. He graduated from the literary department of the University of Michigan in 1888 and from the Detroit College of Medicine in 1892. He was elected a Fellow of the American College of Physicians in 1917.

Dr Hickey was one of the pioneers of Roentgenology. At the time of the discovery of the Roentgen ray, 1895, he was practicing the specialty of laryngology and rhinology in Detroit, and was a teacher of pathology at the Detroit College of Medicine, and pathologist to the Detroit Clinical Laboratory.

An expert amateur photographer he quickly visioned the future of the X-ray in medicine, and urged upon the directors of the Clinical Laboratory the equipment of an X-ray Department that would make the new diagnostic method available to the general profession. This was the first medical X-ray apparatus, using the Ruhmkorff coil installed in Michigan and one of the earliest in the country. The field of usefulness of the X-ray

in diagnosis and therapeutics rapidly grew and Dr Hickey soon was compelled to devote all his time and energy to his new specialty

He was Professor of Roentgenology in the Detroit College of Medicine from 1909 to 1922. During this period he developed into a national authority on radiology, and was a member of all the radiological societies of the country.

He was commissioned Lieutenant Colonel in the Medical Corps of the United States Army in the World War and was in command of X-ray equipment service of the A E F, with headquarters at Paris.

In 1922 Dr. Hickey was appointed Professor of Roentgenology at the University of Michigan, which position he held until his death. A sound, conservative and convincing teacher, his happiest moments were spent with his students in laboratory and classroom. He had a charming personality and attached to himself a host of friends in this country and abroad, who deeply regret his death.

—Furnished by Charles G Jennings, M D, (Master), Governor for Michigan

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Dr Wm A Jenkins died at his home, 1626 Cherokee Road, Louisville Ky Dec. 17th 1930, of Lymphosarcoma. A native of Kentucky, he attended the public schools of that

state, graduated from Hanover College, Indiana, receiving his Master's Degree, and his medical degree from the University of Louisville in 1897. He located in Louisville after his graduation and continued practice in that city until his death.

He was a member of the staffs of the Baptist, St Anthony's, Deaconess, Kosair Crippled Children and Louisville Municipal Hospitals. He was a member of the Jefferson County Medical Society, Kentucky State Medical Association, American Medical Association, Southern Medical Association and the American College of Physicians. He was a member of the Delta Tau Delta and the Phi Chi Fraternities. He was professor of medicine in the University of Louisville from 1908 to 1923, when he became professor of clinical medicine and occupied that chair to the time of his death. During the world war he joined the medical corp and continued with rank of major until after the Armistice. He was also a member of the Medical Reserve Corp with the rank of colonel.

He confined his professional activities to internal medicine and enjoyed a large consultation practice. His energy, integrity and rare intellect fitted him eminently as a professor and clinician and attained for him a high position in medical circles in the mid-west and south.

# The Glycosuria of Hyperthyroidism and Its Clinical Significance\*

By I. M. RABINOWITCH, *Montreal*

**G**LYCOSURIA is not infrequently met with in cases of hyperthyroidism. As in pregnancy, however, if urinalyses are made at frequent intervals rather than on special occasions, its incidence is found to be much greater than recorded in standard text books. It is somewhat related to the basal metabolic rate, the higher the rate, the greater is the incidence. This probably accounts for the fact that glycosuria is met with more frequently in exophthalmic goitre than in so-called "secondary" hyperthyroidism associated with adenomata. The relationship between basal metabolism and glycosuria will, again, be referred to, as the above statement requires modification. The literature on this subject is quite extensive. However, as it is readily available, in review form<sup>1,2,3,4</sup>, and for purposes of brevity, no summary of it will be given here, with the exception of reference to relevant facts.

When glycosuria is found, the determination of the cause is more than of academic interest, as it influences treatment. In hyperthyroidism, when the rate of metabolism is markedly in-

creased, there may be marked destruction of vital body tissue namely, protein, as shown by the excretion of urinary nitrogen (Urinary nitrogen is a reliable index of protein metabolism). With destruction of large quantities of protein a vicious circle may result, since protein utilization per se, may, because of its specific dynamic action, be responsible for increased rate of metabolism. Thus, increased metabolism due to hyperthyroidism leads to increased protein destruction and increased protein destruction further increases metabolism. Much of body protein may be conserved in such cases and rate of metabolism thereby lowered by administration of diets of high carbohydrate content, because of their protein sparing effects. On the other hand, if the glycosuria is due to diabetes, the use of such diets, without the use of insulin, would be harmful.

From the clinical picture alone, it is impossible in the great majority of cases, to determine the cause of the glycosuria, as the signs and symptoms of hyperthyroidism and diabetes may be quite similar. As a matter of fact the more marked the hyperthyroidism, the more do the signs and symptoms of this disease simulate those of diabetes. For example in both cases there may

\*From the department of Metabolism The Montreal General Hospital Montreal Canada



be marked weakness, loss of weight, polyuria and thirst. When the hyperthyroidism is more marked and the metabolic rate is very high, in addition to the above mentioned signs and symptoms, one may find flushed skin, increased pulmonary ventilation, a rapid and bounding pulse and, the urine, in addition to containing sugar, may, also, contain acetone and diacetic acid. In other words, the signs and symptoms of severe hyperthyroidism may be almost identical with those of severe diabetes with acidosis. As a matter of fact, Wilder<sup>2</sup>, who has had a very wide experience with both diseases, suggests the use of iodine in severe cases of diabetes as a therapeutic test to rule out thyroid disease. In diabetes, uncomplicated by hyperthyroidism, iodine is without observable effects.

There is additional reason for determining the true cause of the glycosuria. If it is due to hyperthyroidism only, with the disappearance of the latter, following thyroidectomy or other measures, the glycosuria also disappears. Should the glycosuria have been attributed to diabetes, in such a case, it is obvious that one would regard the diabetes as having been cured. As a matter of fact, the literature is not without such "cures." Authentic cases of cured diabetes, if there are any at all, are extremely rare.

Judging from the literature, there is no uniform procedure for differentiating the glycosuria of hyperthyroidism from that of diabetes. One of the most common methods made use of is the study of fasting and post-prandial blood sugars. In the latest edition of his "Treatment of Diabetes" Joslin<sup>4</sup>

states that "Ordinarily a patient is said to have diabetes who has certain characteristic symptoms, glycosuria varying with the diet and hyperglycemia above 0.13 per cent before or above 0.16 per cent after a meal. For the purposes of differentiating between the glycosuria of diabetes and of hyperthyroidism and in order to avoid premature diabetic cures, we have raised the standard for a diagnosis in hyperthyroidism to a blood sugar of 0.15 per cent fasting and 0.20 per cent or more after meals in addition to glycosuria." Marsh<sup>5</sup> makes use of simultaneously determined respiratory metabolism and blood sugar time curves. John<sup>3</sup> uses blood sugar time curves only. We, in addition to the method described by Marsh, make use of another procedure, the details of which will presently be discussed. It is based upon Allen's Paradoxical Law, namely, that, in the absence of true diabetes, there is no limit of tolerance for carbohydrates—the more given the more is utilized. This procedure is of special value because of its applicability in general practice and will be described later in detail.

The belief that the glycosuria of hyperthyroidism differs fundamentally from that of true diabetes is so general, one would hardly be justified in renewing the discussion, were it not for the new views recently advanced by John<sup>3</sup>. This author is apparently quite convinced that the hyperglycemia and glycosuria noted in this disease are the result of defective oxidation of carbohydrates and this defective oxidation is attributed to defective insulin production. In other words, it is implied that we are dealing essen-

tially with a diabetic condition. Because of this view, John warns that it is a very serious matter to disregard such glycosuria. If this view is correct, the present practice of giving such patients high carbohydrate diets without insulin is obviously not logical. It is, therefore, important to reconsider this subject.

The practical value of explanations of clinical phenomena may be said to be directly proportionate to their support by clinical experience and experimental facts. In support of his views, John quotes the extensive literature which includes theoretical, clinical and experimental data. It is, however, of interest here to note that from the same data made use of by John, it is possible to draw diametrically opposite conclusions.

#### ANATOMICAL CONSIDERATIONS

As anatomical evidence to support his views, John quotes the findings of Holst<sup>6</sup>, Rohdenberg<sup>7</sup>, Garrod<sup>8</sup>, Marinesco and Parhon<sup>9</sup>, Falta<sup>10</sup> and Lorand<sup>11</sup>. From these, he concludes that there is a casual relationship between Graves' disease and diabetes. To quote verbatim, "There is reason to believe that in Graves' disease the well known anomalies in sugar metabolism are induced by gross anatomical changes in the pancreas etc." With respect to this two observations may be made. Firstly, the fact that histological changes in the pancreas may be found in Graves' disease is not necessarily proof that the association is causal; it may be accidental. Strongly suggestive that it is accidental are the low incidence of diabetes amongst individuals suffering from Graves' disease and the

low incidence of a history of Graves' disease amongst diabetics. John in an excellent review, tabulates the cases of combined diabetes and hyperthyroidism, according to the literature from 1867 to 1927. In all there were 137 cases. In the latest edition of his "Treatment of Diabetes" Joslin reports 75 such cases amongst 4917 diabetics. Joslin, also, quotes Wilder who, amongst 1249 cases of diabetes found 11 per cent "primary" hyperthyroidism and 18 per cent of "secondary" hyperthyroidism. According to these percentages, there were approximately 36 cases of combined hyperthyroidism and diabetes amongst 1249 diabetics. Amongst the 3000 diabetics, in our clinic, there are 24 cases.

Opposed to the histological findings referred to are the negative findings of others. It may here be observed that the cases particularly of value in such investigation are, obviously, not those of diabetes and hyperthyroidism combined but of hyperthyroidism alone. Our pathologist Dr L. J. Rhea, tells me that in a careful study of ten fatal cases of Graves' disease nothing significant could be detected in the pancreatic tissues\*. These findings are identical with those of Joslin<sup>1</sup> who quotes Shields Warren and concludes that "The whole question deserves re-investigation". Apropos of positive findings, Shields Warren who has had an exceptional experience with the pathology of diabetes very aptly points out in his excellent monograph on the subject<sup>12</sup> that "It is important to keep

\* A-23-70 A-25-143 A-25-293 A-25-32  
A-26-27 A-26-100 A-27-176 A-27-25 A-27-  
233 A-29-169

in mind the great difficulties facing any estimate of the number of islands present in the human pancreas and the wide range in number of islands known to be present normally. In a study of five autopsied cases of diabetes associated with hyperthyroidism, the same author, found the islands of Langerhans were negative in all except one case and concludes "There is absolutely no characteristic picture."

Assuming, however, that positive findings are frequent and causal, it does not necessarily follow that diabetes and hyperthyroidism are related. It has been repeatedly emphasized that anatomical and functional integrity are not necessarily synonymous terms. The most one can conclude from the anatomical data is that there appears to be a functional relationship between the thyroid and the pancreas. For this, however, no anatomical evidence is necessary. For example, physiologists demonstrated sometime ago that in the regulation of the blood sugar the pancreas, thyroid and other organs of internal secretion (adrenal and pituitary bodies, etc.) are intimately concerned. Thus, thyroidectomy enhances the action of insulin, rabbits have been found to be 3 to 9 times as sensitive to insulin as before operation. However, after thyroidectomy, rabbits are also less sensitive to adrenalin. Also following removal of the adrenal bodies, the characteristic hyperglycemic response to stimulation of the Claude Bernard centre is not obtained. These findings led to the suggestion that the adrenal bodies are the active agents in the production of hyperglycemia. Adrenalin is secreted into the general circulation, reaches the liver by the

hepatic artery as well as the portal vein and also enters the muscles and mobilizes the sugar there. The adrenal bodies will, again, be referred to in dealing with signs and symptoms. Other and more recent experiments of Burns and Marks<sup>1</sup> and Bodinsky<sup>14</sup> and similarly suggestive are discussed by Joslin<sup>1</sup>

#### CLINICAL CONSIDERATIONS

A clinical fact which remains to be explained is that in many cases, according to the literature, the history of diabetes followed, rather than preceded, the history of hyperthyroidism. It may, however, here be observed that diabetes following hyperthyroidism and diabetes caused by hyperthyroidism are, obviously, not synonymous terms. As a matter of fact, a careful study by the writer of the cases reported failed to reveal, according to our present standard methods of studies, an authentic case of diabetes resulting from hyperthyroidism. In our hospital with a fairly large Goitre Clinic, Dr. E. M. Eberts, who is in charge, tells me he knows of no such case from his follow-up records. Glycosuria, except when regarded as due to diabetes before operation, disappeared after operation. These results are stressed since such patients are not subjected to diabetic management, not only are carbohydrates not restricted in the diets of such patients, but they are encouraged. The histories alone may be suggestive but it may here be observed that one is not justified in drawing conclusions from them for the following reasons —

To conclude, in a given case, that diabetes was caused by hyperthyroid-

ism, it is important to definitely demonstrate that the individual was not a potential or mild diabetic prior to the onset of the hyperthyroidism. Histories, carefully, as they may be taken, are misleading. In potential, and in the early stages of chronic progressive diabetes, as is generally recognized, there are, as a rule, no signs or symptoms. The glycosuria is usually discovered accidentally during the course of a routine examination for life assurance or for some other purpose. It is, also, generally recognized that potential diabetes may be made active and mild diabetes may be converted temporarily or even permanently into a severe form, by an injury, operation or any other illness. Does this explain the diabetes which developed subsequently to operation for hyperthyroidism in the cases referred to by Joslin?<sup>2</sup>

#### EVIDENCE BASED UPON BLOOD AND URINARY SUGAR DATA

Soon after the introduction of thyroid preparations in medicine, Dale James<sup>15</sup> in 1894 first pointed out that their continuous use led to the appearance of sugar in the urine and that the sugar promptly disappeared on the drug being discontinued. In his "Zuckerkrankheit" von Noorden refers to the frequent occurrence of this form of glycosuria, but does not attribute it to diabetes. He believes that thyroid feeding merely elicits the presence of a pre-diabetic condition. Though hyperthyroidism particularly Graves disease and conditions which result from administration of thyroid preparations are not exactly similar a large part of the signs and symptoms of hyperthyroidism can be duplicated by

feeding these substances. This observation led to a series of investigations. The literature is quite extensive and stages of fundamental importance only will be referred to. The methods of investigation may be divided into four types, namely, (a) studies of glycosuria only, (b) blood sugar studies, (c) respiratory metabolism, and (d) combination of all three methods.

Wilder and Sansum<sup>16</sup> have shown that when glucose is injected intravenously at uniform rates glycosuria occurs more readily in hyperthyroid than in normal individuals. Later, however, Wilder<sup>2</sup> pointed out that this does not prove that there is anything at fault with oxidation. As defective oxidation of carbohydrates is regarded as a fundamental disturbance in diabetes, it cannot be concluded from these results alone that an individual is suffering from this condition. John takes exception to this view, as during these experiments, blood sugar data were not obtained. "The conclusion" he contends "is valid only if it can be proved that in the cases of hyperthyroidism in which glycosuria appears, only the permeability of the kidney for sugar is changed." In other words it is implied that if hyperglycemia accompanies these experiments, the individual has diabetes.

Just as it is difficult to interpret results of physiological experiments where urinary sugar only is studied, so are difficulties met with clinically. Blood sugar studies are essential but as will presently be shown their interpretation is not simple. In hyperthyroidism the blood sugar may be very misleading.

About a decade ago, prior to the presently available bedside facilities for basal metabolic rate determinations, blood sugar time curves were widely made use of in the diagnosis of hyperthyroidism. These tests were based upon the fact that the glycosuria of hyperthyroidism depends upon hyperglycemia. As hyperglycemia precedes glycosuria (in the absence of the low renal threshold) the value of its detection is obvious. In the majority of cases, however, in the absence of diabetes, hyperglycemia is very uncommon when bloods are collected in the fasting state. Blood sugar time curves were, therefore, made use of. It is generally recognized that following glucose ingestion, blood sugar time curves may detect abnormal carbohydrate metabolism long before there is hyperglycemia in the fasting state.

The curves obtained in hyperthyroidism are not unlike those found in diabetes, in so far as the maintained elevation of the blood sugar is concerned. The first extensive report of such curves was that of Denis, Aub and Minot<sup>17</sup> in 1917. The results obtained, when correlated with the clinical conditions, were not uniform. Though, following either thyroidecto-

my or other therapeutic measures which led to relief, the blood sugar levels tended to be lower, there was no definite relationship between the levels and the basal metabolism. These authors did not regard these abnormal curves as indicative of diabetes. Since then a large number of similar observations have been made by different workers with varying results. Characteristic findings may be seen in one of our most recent cases.

It will be noted that as the degree of hyperthyroidism decreased, as measured by the basal metabolic rate, there was also improvement of carbohydrate metabolism, when the basal metabolic rate was +50 per cent not only was there a mild grade of hyperglycemia in the fasting state but, at the end of two and one-half hours, there was still marked elevation of the blood sugar, whereas, seventeen days later when the basal metabolic rate had decreased to +28 per cent, not only was the blood sugar in the fasting state normal, but it was also normal at the end of the test. There was, however, hyperglycemia at the end of the two hour period, though of a much lesser degree than at the first test.

Valuable as such data may have

HOSP No 2806/30

May 28th B M R +50 per cent

Fasting

30 minutes after ingestion

60 " " "

120 " " "

150 " " "

0.128 per cent

0.212 per cent

0.256 per cent

0.312 per cent

0.285 per cent

June 14th B M R +28 per cent

Fasting

30 minutes after ingestion

60 " " "

120 " " "

150 " " "

0.119 per cent

0.217 per cent

0.238 per cent

0.188 per cent

0.109 per cent

been prior to the era of routine basal metabolic rate determinations for the diagnosis of hyperthyroidism, they are of relatively little value in order to settle the problem as to whether glycosuria found in a given case of hyperthyroidism is, or is not, of diabetic origin. According to John such curves suffice, since, to quote verbatim "Hyperglycemia is the result of faulty oxidation of glucose." This view expressed will, again, be referred to. Direct proof, however, that in hyperthyroidism, in the absence of true diabetes, there is no defective oxidation of carbohydrates may be found in the experiments first recorded by Du Bois<sup>18</sup>, then by Sanger and Hun<sup>19</sup>, by Richardson<sup>20</sup> and later by Marsh<sup>5</sup>. These observations clearly demonstrate that not only are individuals suffering from hyperthyroidism able to oxidize carbohydrates as readily as a normal individual, but they apparently utilize sugar with marked avidity. In the cases reported there was no glycosuria with ordinary diets.\* That individuals with hyperthyroidism also oxidize carbohydrates very readily even when they manifest hyperglycemia and glycosuria, in the absence of diabetes, may readily be seen from one of our cases recorded in Table 1. The data represent respiratory metabolism and blood sugar time curves obtained simultaneously following the ingestion of 100 grams of glucose.

This is our routine procedure in cases of glycosuria of doubtful origin

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\*In five of the cases investigated by Sanger and Hun, glycosuria was found only after glucose ingestion. In Case No. 5 studied by Du Bois, a trace of sugar was found on one occasion only.

Though the data appear formidable, the technique, once it is perfected, is simple. As the details were previously reported in a study of renal glycosuria<sup>21</sup>, and for purposes of brevity, they will not be repeated here. An observation may, however, here be made with regard to the calculation of the non-protein respiratory quotients.

For the calculation of the non-protein respiratory quotients, the urines are not collected periodically, as this, from experience, has been found to be impossible, unless the individual has marked polyuria or is given large quantities of water. The latter procedure, however, leads to the washing out of stored nitrogen and the error from such practice may be much greater than when one sample of urine is obtained at the end of the test and the amount of nitrogen excreted per hour is calculated on the assumption of a uniform rate of excretion. With the latter procedure, there is also a lesser tendency to disturb the patient—a very important matter in respiratory work.

Briefly, the data in Table 1 demonstrate that, in hyperthyroidism, without diabetes, there is no disturbance of carbohydrate oxidation, in spite of hyperglycemia and glycosuria. As a matter of fact, in this particular case, carbohydrates were oxidized very rapidly, when hyperglycemia was at its maximum. This is shown by (a) the respiratory quotients, (b) the rate of oxidation of glucose (grams per hour) and, (c) the percentage increase of heat production above the basal level (specific dynamic action).

It is interesting here to note the high urinary nitrogen. During a period of three hours with no intake of nitrogen,

there was an excretion of 1.26 grams or approximately 10 grams per twenty-four hours. This is a characteristic of hyperthyroidism and is found only in diabetes when there is marked emaciation or acidosis. In this case, there was marked emaciation, but no acidosis. With marked emaciation in diabetes, however, one would not observe such high respiratory quotients and, in the absence of treatment, the blood sugar would certainly not be normal in the fasting state.

Data of the nature just presented including the work of such authorities as Du Bois and Richardson are not however acceptable, according to John, as proof of the absence of diabetes. This is shown by the following explanation, as suggested by John, for the above mentioned results:

"This one would expect, for if the total oxidation of the body is increased in cases of hyperthyroidism, as is shown by the high metabolic rate, then the rate of combustion of carbohydrate must also be increased. Moreover, this higher rate of combustion of carbohydrate will continue until the islands of Langerhans can no longer supply a sufficient quantity of insulin to cope with the increased demand. In other words, in hyperthyroidism there is a hyper-secretion of insulin which lasts as long as the islands of Langerhans can stand the demand on them. In the early stage of hyperthyroidism, as is stated by these authors, there is only this increased metabolic function, a sort of last rush of flames before the fire dies down. Carbohydrate (and protein and fat as well) are burning with a greater intensity, as the R Q curve shows, the R Q falling only at

a later stage when the islands are becoming exhausted and are no longer able to supply a sufficient amount of insulin . . . etc."

I find it rather difficult to follow the above arguments. The rapid oxidation of carbohydrates, it is stated, is to be expected if the total oxidation of the body is increased; if the rate of metabolism is increased, then the rate of combustion of carbohydrates must also be increased. This view does not conform to experience; the rate of metabolism and the rate of oxidation of carbohydrates in uncontrolled diabetes, that is, when glycosuria is present, have never been found, according to the literature, to be parallel. Another view, it will be noted, is that the falling respiratory quotient in the late stages of hyperthyroidism is an index of the exhaustion of the islands of Langerhans. Low respiratory quotients are undoubtedly found in advanced cases of hyperthyroidism. These, however, may be readily explained on the basis of exhaustion of glycogen reserve rather than defective carbohydrate oxidation. Proof of this may be seen in Table 2. This was a case of severe hyperthyroidism without glycosuria. It will be noted, following glucose ingestion, that there was a marked rise of the respiratory quotients and increased utilization of carbohydrates. If the low quotient found in this case in the fasting state was due to exhaustion of insulin, such rates of oxidation of carbohydrates as found would hardly be possible.

It may be observed that in the two cases reported here (Tables 1 and 2) we have a possible explanation of the occurrence of glycosuria in one case of hyperthyroidism and its absence in







another and also an explanation of the lack of parallelism noted at times between the levels of blood sugar time curves and rates of metabolism. A fundamental difference, according to Allen, between the glycosuria of hyperthyroidism and that of diabetes, is that though in both cases, glycosuria depends upon hyperglycemia, in diabetes the glycosuria is independent of the glycogenic content of the liver. In other words, unlike in diabetes, in order to produce glycosuria in hyperthyroidism, the patient must have a good store of glycogen. Since the storage of glycogen tends to be exhausted in severe cases and in cases of long duration, one would expect, in such cases, a high metabolic rate and no glycosuria, whereas, with hyperthyroidism of short duration one may expect a parallelism between the glycosuria or level of the blood sugar time curve and the basal metabolic rate, as the glycogen reserves have had relatively less time to be exhausted.

Respiratory data add further proof that the glycosuria of hyperthyroidism is not the same as that of diabetes. In diabetes, there is not only evidence of defective oxidation of carbohydrates, but there is much to suggest that storage of carbohydrates is also at fault. If, therefore, it can be shown that the glycosuria of hyperthyroidism is the result of defective storage, one might then suggest a causal relationship between the two conditions. Sanger and Hun<sup>10</sup> unable to explain their experimental results on the basis of defective oxidation, suggested defective storage. It is, therefore, interesting here to note the recent observations of Richardson, Levine and du Bois.<sup>22</sup> By an ingenious

experiment, these authors have been able to demonstrate that defective storage of glycogen need not be made use of as an explanation of the blood sugar time curves in hyperthyroidism. The glycogen reserves of two patients suffering from exophthalmic goitre were studied and were estimated to be at least as great as normal. Evidence was presented against the theory that there is any defective mechanism by which glycogen is stored in this condition. These authors suggest that the blood sugar time curves observed might be explained on the basis of unusually rapid or complete absorption of sugar from the intestines or to a temporary increase of glycogenolysis. Having, therefore, eliminated both defective storage and defective oxidation to account for the glycosuria of hyperthyroidism, there is little left of an experimental nature to support the view that there is a causal relationship between this disease and diabetes.

As the above conclusion is based practically upon the identical data made use of by John, it is obvious that the different conclusions are not the result of experiment, but of interpretation. It is, therefore, necessary to find wherein there is disagreement. This is clearly shown in John's interpretations of his own blood sugar curves and in his criticisms, particularly of the work of Wilder and Sansum, of Sanger and Hun and of Marsh. The presence or absence of hyperglycemia appears to be the critical differentiating point between diabetic and non-diabetic glycosuria, hyperglycemia and diabetes are apparently regarded as synonymous. Thus, with regard to blood sugar curves, it is stated, to quote verbatim,

"I cannot but feel that a protracted hyperglycemia after the ingestion of a large dose of carbohydrate means that the body is unable to supply insulin in sufficient quantity to transform this carbohydrate into glycogen to be stored in the liver and muscles, and bring about its proper oxidation," and, again, "A study of tolerance tests shows a range of response from the perfectly normal to that which *indicates* the presence of severe diabetes. There is no definite line of demarcation between the normal and the diabetic state, and no matter where one might put a dividing line, *the high incidence of diabetes would still be evident.*" "Hyperglycemia," John insists, "is the result of faulty oxidation of glucose in the body" and his criticism of Marsh's work is particularly worthy of note here. Marsh, because of his simultaneously determined respiratory metabolism and blood sugar time curves does not attribute the hyperglycemia and glycosuria noted to defective oxidation of carbohydrates. With regard to this, John makes the following observations: "If we are to accept Marsh's conception, where are we to draw the line between diabetic and non-diabetic hyperglycemia and glycosuria?" and, later on, "Why does Marsh advocate the glucose tolerance test as a means of differentiating the thyroid glycosuria from diabetic glycosuria and then disregard his own figures?" With regard to the latter conclusion, it is obvious, at least to the writer, that Marsh's purpose in reporting the particular case referred to was to demonstrate that, in exophthalmic goitre, even when hyperglycemia is at its maximum, oxidation of carbohydrates, unlike in diabetes, may also be at a maximum.

#### INTERPRETATION OF BLOOD SUGAR DATA

An important fact which appears to have been overlooked by John is that with blood sugar time curves as with other laboratory tests, a variety of conditions may be responsible for similar results. Interpretation of laboratory tests depends upon recognition of underlying physiological principles. It is quite true that hyperglycemia is a characteristic response to the ingestion of glucose in diabetes. Hyperglycemia is, however, also, found in conditions other than diabetes and there is much evidence that in these conditions and in diabetes the mechanism of its production is not the same. For example, hyperglycemia and glycosuria may be produced in normal individuals by the injection of adrenalin and, when hyperglycemia is at a maximum, respiratory metabolism data clearly demonstrate that carbohydrates are being oxidized very readily\*. This is contrary to experiences with diabetes. Allen's<sup>23</sup> observations with regard to adrenalin may here be referred to: "With adrenalin glycosuria, much of the injected dose of dextrose may be utilized at the height of the glycosuria and the utilization increases with increase of dose. The glycosuria is not a diabetes and does not depend upon the inhibition of the pancreas nor upon neutralization, destruction or inefficiency of the internal pancreatic secretion." This Allen states also implies to the thyroid.

Adrenalin is particularly mentioned as an example, because the writer is of the opinion that many of the signs and symptoms of hyperthyroidism are due to this internal secretion. There is much to support this view. Excess

\*Unpublished data

quantities of adrenalin in the circulation have been reported and some of the signs and symptoms of hyperthyroidism are not unlike those following adrenalin injection, namely, the mental confusion, tachycardia, palpitation, glycosuria and the peculiar pulse pressure-pulse rate relationship. The latter phenomenon is particularly worthy of note. As is well known, injection of adrenalin results in an increased pulse rate accompanied by increased pulse pressure. As far as the writer is aware, an increased pulse pressure accompanied by an increased pulse rate is found in hyperthyroidism only, if we exclude aortic disease and congenital or other cardio-vascular abnormalities (arterio-venous aneurism, etc.)

#### APPLICATION OF ALLEN'S PARADOXICAL LAW TO DIAGNOSIS

Simultaneously determined respiratory metabolism and blood sugar time curves, because of the technique involved have obviously limited use, as such curves can be made use of in hospital practice only. They represent part of our routine procedure in the diagnosis of doubtful cases of glycosuria. A much simpler procedure, however, and equally reliable, in our experience, is the application of Allen's Paradoxical Law. Briefly, this Law is that the more sugar is given to non-diabetic individuals, the more is utilized. As Allen puts it, "Limits of tolerance in non-diabetic animals are all apparent, not real, there is no real limit of the power

of utilization of sugar, except death.

The Paradoxical Law of dextrose distinguishes sharply between diabetic and every type of non-diabetic animals. The limits of tolerance in diabetic animals are real and not apparent. In totally diabetic animals, an injection of dextrose causes an increment of glycosuria not only equal to, but frequently greater than, the injected dose. In milder diabetes, not only is the proportion of excreted to injected dextrose generally high, but the assimilation may be made worse instead of better by an overdose—just the opposite of the Paradoxical Law." Allen<sup>23</sup> first suggested that this Law may be found of service to clinical tests of diabetes and suggested that it is probably more specific for decision between active diabetes and other forms of glycosuria which may imitate it, than detecting incipient diabetes in its earliest stages. In our routine, the individuals are given diets of constant composition with respect to protein and fat and the amounts of carbohydrates are increased daily by the administration of glucose in small amounts at frequent intervals. An example is shown in Table 3.

J.A., a male, (Hosp No 3475/29), age 53 yrs, was referred to the department of metabolism by Dr R. R. Fitzgerald on July 3rd, 1929. He was suffering from hyperthyroidism and manifested the typical signs and symptoms of exophthalmic goitre. There was a history of glycosuria prior to his admission. On account of the latter, a blood sugar time curve was obtained with the following results —

Period	Blood Sugar	Urine Sugar
Fasting	0.113 per cent	"
30 minutes after ingestion	0.217 "	"
60 " "	0.263 " "	trace
120 " " "	0.181 " "	trace
150 " " "	0.161 " "	0

T A B L E 3  
DIET DEMONSTRATING ALLEN'S PARADOXICAL LAW.

Hosp No 3475/29				Male		53 years		
Date	U R I N E			D I E T.				
	sugar	acetone bodies	nitrogen	B M R	Blood sugar (fast- ing) %			
July 5th								
6th	+	tr		+56	125	150	60	Lugol's iodine 0.5 cc t.i.d.
7th	tr	tr			125	150	60	
8th	tr	tr			125	150	60	
9th	tr	0			0.133	150	60	
10th	0	0	12.5		125	150	60	
11th	tr	0	11.5		225	150	50	
12th	tr	0	9.8	+33	325	150	50	Glucose 20 gms every hour for 10 hours
13th	tr	0	5.3?		325	150	50	Glucose 20 gms every hour for 10 hours
14th	0	0			425	150	50	Glucose 30 gms. every hour for 10 hours
15th	tr	0	6.73		425	150	50	Glucose 30 gms every hour for 10 hours
16th	0	0		+16	425	150	50	Glucose 30 gms ever. hour for 10 hours
17th	0	0			425	150	50	Glucose 30 gms every hour for 10 hours
18th	0	0			425	150	50	Glucose 30 gms ever. hour for 10 hours
19th	0	0		+10	425	150	50	Glucose 30 gms ever. hour for 10 hours
20th	0	0			425	150	50	Glucose 30 gms every hour for 10 hours
21st	0	0			425	150	50	Glucose 30 gms every hour for 10 hours
22nd	0	0			425	150	50	Glucose 30 gms ever. hour for 10 hours

On admission, there was, again, glycosuria and, as there was no acetoneuria, Allen's Paradoxical Law was applied. Observations were made with regard to the relationship between (a) intake and output of sugar, (b) glycosuria and nitrogen excretion, and (c) glycosuria and basal metabolism.

As pointed out before, nitrogen excretion may be markedly increased in these cases. However, if the individual can oxidize glucose very well, that is, if he is not a diabetic, the administration of large amounts of glucose will tend to have a protein sparing effect and thus cause a decreased excretion of nitrogen. Should the glycosuria be due to diabetes, the same effect can be obtained only with the use of insulin. The following are to be noted (Table 3).

- (a) No relationship whatever between the intake and excretion of sugar, as a matter of fact, traces of sugar only were found when the diet was increased to 425 grams of carbohydrate daily.
- (b) In spite of huge quantities of carbohydrates, the blood sugars were persistently normal in the fasting state, except on one occasion (July 8th, 1929) when there was a mild grade of hyperglycemia, namely, 0.133 per cent.
- (c) Sugar had a protein-sparing effect when the basal metabolic rate was still above normal. The daily intake consisted of approximately 8 to 9 grams of nitrogen. It will be noted that up to July 12th, the excretion was

greater than the intake, the body proteins were being conserved.

Beyond the last date recorded in the Table, the case is of no further interest with respect to the subject matter. A thyroidectomy was performed and the patient made an uneventful recovery.

#### SUMMARY

The conclusion which the writer draws from all of the above observations is that the glycosuria of hyperthyroidism is not of diabetic origin. Clinical experience alone, however, would appear to suffice, in order to draw this conclusion, as the glycosuria of such individuals disappears after successful management of the hyperthyroidism. This finding is stressed, in view of the fact that not only are such patients allowed unrestricted diets, but large quantities of carbohydrates are actually encouraged. This would, obviously, not be the course of a potential or active diabetic when exposed to such treatment. It is hardly necessary, however, to point out that, glycosuria, when met with in case of hyperthyroidism, should always be given serious consideration, as amongst such individuals there may be true diabetes. Simultaneously determined respiratory metabolism and blood sugar time curves and the application of Allen's Paradoxical Law help in the differential diagnosis.

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# Extra-Insular (Central) Glycosuria With Hyperglycemia Following Epidemic Encephalitis

By DR I W HELD, DR A ALLEN GOLDBLOOM and  
DR JULIUS CHASNOFF, (*Beth Israel Hospital*), *New York*

SINCE the epoch-making discovery of von Mering and Minkowski<sup>1</sup> in 1889 that a lesion in the islands of Langerhans is responsible for diabetes mellitus and the much more recent discovery of Banting and Best<sup>2</sup> that insulin has a favorable effect on this condition, the tendency to ascribe every case of glycosuria and hyperglycemia to either functional or pathologic changes in the islands of Langerhans has been pronounced. However, it is possible for these conditions to occur without involvement of the islands of Langerhans and we feel that when one encounters such a case of hyperglycemia or glycosuria of non-insular origin it is of sufficient interest to be reported. The differentiation between the two is not a purely academic matter. It is highly important from both the prognostic and the therapeutic standpoint.

## CASE REPORT

Mrs R C, age 37, was admitted to the Beth Israel Hospital, June 6, 1929.

*Chief Complaints* Dizziness, generalized swelling, elimination of great quantities of urine and excessive thirst accompanied by bitterness and dryness in the mouth.

*Past History* Two abortions, one two years before admission, the other one year before admission. The patient had one child (8 years old) in a marriage of ten years. Past history otherwise unessential.

*Present Illness* According to the history given by the family physician, Dr H Lesser, who referred the case to the hospital, the patient became ill one month before admission. She had had symptoms of a mild infection interpreted as influenza and from which she apparently recovered. A few days later, however, she began to complain of dryness of the mouth and extreme thirst that compelled her to partake of excessive fluids and void large quantities of urine. A generalized swelling of the face and body appeared, especially noticeable over the extremities. This diminished somewhat while she was confined to bed. She became drowsy, sluggish, weak and dizzy. Her skin became coarser in texture and darker in color. There was a generalized eruption, particularly over the face, chest and back. The patient was sent into the hospital with the diagnosis of diabetes mellitus with impending coma.

*Physical Examination* The patient is a well developed, obese woman lying comfortably in bed, well oriented and co-operative. Her scalp is dry with thinning hair. Her face shows diffuse eruptions, chiefly of discrete, small papulopustular lesions with reddish areolae, extending down onto the chest anteriorly and posteriorly. The skin, generally, is very rough and is dark in hue. The dependent parts, like the breasts, and extremities show cutis marmorata. The skin lesion was diagnosed by Dr Oscar Levine as hydrocystoma and folliculitis.

Examination of the mouth revealed mild pyorrhea, particularly around the capped teeth, the tongue was coated, the throat congested; the thyroid was not palpable and there was no adenopathy. Both ear regions



were prominent due to swelling of the soft tissues. Chest examination was negative. The heart was slow and regular. Blood pressure was 154/76. Palpation of the abdomen showed a slight enlargement of the liver, but it was otherwise negative. The edema was not a pitting one but was very hard and tense. In the presence of a dry skin, it gave the impression of the type encountered in myxedema. There was no pallor of the skin, which was rather uniformly dark brown and extremely rough. There was no girdle obesity. The reflexes were normal except for diminished knee jerks. The pupils were equal, regular, and reacted to light and accommodation. There was no disturbance of vision, the eye-grounds and field of vision were normal, as confirmed by Doctors Torok and Slomka. A complete neurologic examination by Dr. E. P. Goodhart was negative. The temperature varied from 99° to 101°, being lowest at 6 A. M., highest at 2 P. M. On certain days it rose transiently to 102° and 103°. The pulse varied from 70 to 100. The

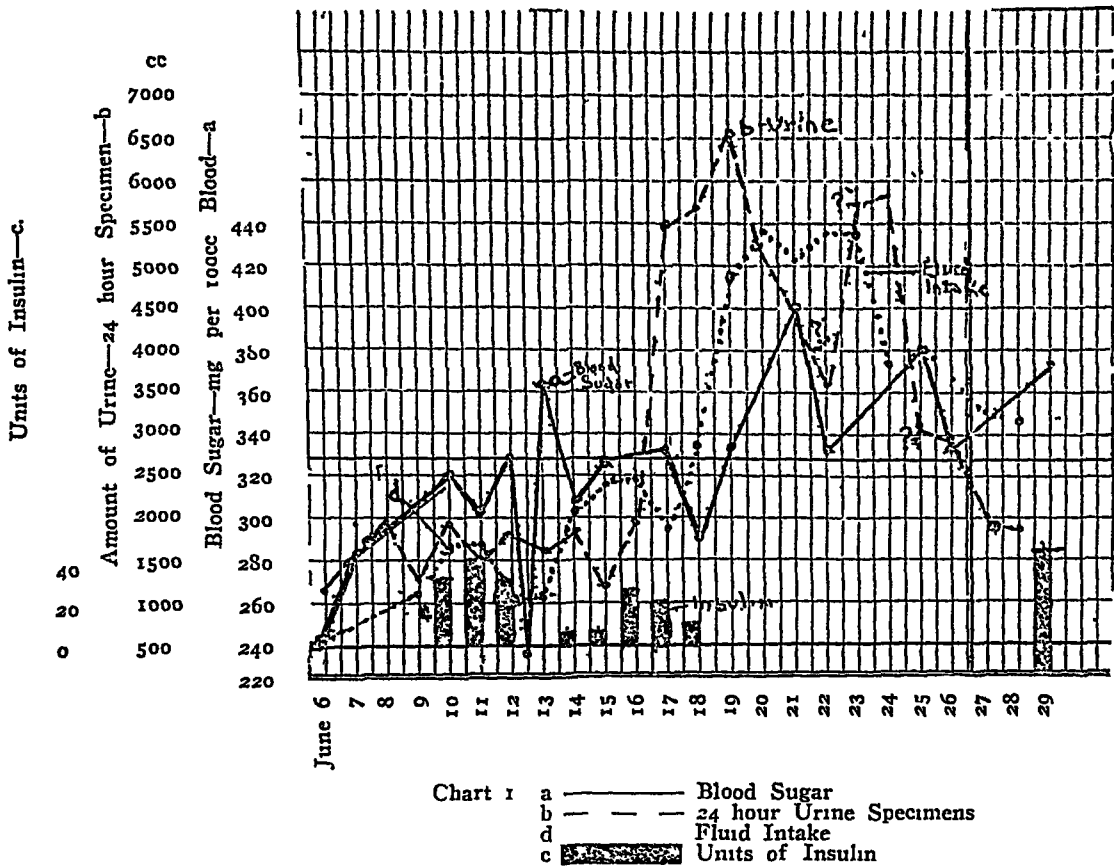
blood pressure varied from 150/100 to 80/60 except on June 23, 1952, when in the pre-arrest state it dropped to 80/44.

**Laboratory Findings.** The urine varied in amount from 45 to 200 oz. daily. The specific gravity fluctuated from 1010 to 1026. The albumin never exceeded +; glucose varied from 0 to +++++. There were no definite microscopic findings. (See Charts I and II).

The blood count showed on the average:

Hemoglobin	75%
R. B. Cells	4,100,000
W. B. Cells	8,000-18,000
Diff. Count:	
Segmented	81%
Stuffs	4%
Small lymphs	10%
Monos	2%
Platelets	165,300

The blood sugar varied as recorded, Charts I and II. The blood chemistry showed non-protein nitrogen 29.0 mgms. per 100 cc. of blood, cholesterol 158 mgs., chlorides 478,



calcium 98, total proteins 680, serum albumin 426, serum globulin 254, ration of albumin to globulin 1.6 normal. The blood Wassermann was negative. The cerebrospinal fluid on June 28, 1929, was under normal pressure, 8 mm. It was clear in color, showed albumin +, globulin slight trace, reduction of sugar 0.114, cells per cu. cm. 1 and lymphocytes, negative Wassermann. Basal metabolism on June 13 was +49, the patient being very excitable. On June 15 it was +11. X-Rays of skull, long bones and chest were negative. The electrocardiographic tracings showed inverted T waves in Leads II and III.

#### TREATMENT

In view of the above findings and the history, the patient was placed on a diet of 1000 cc of milk per diem to determine her carbohydrate tolerance. Despite this low diet, her blood sugar rose to 284 mgms per 100 cc of blood, and the urinary findings were sugar + + +, acetone +. On the day after admission a 24-hour specimen of urine showed 17% sugar (32 grams). The patient was kept on this diet for four days, during which time she showed persistent glycosuria. The diet was then changed to 1000 cc buttermilk, and vegetables. The blood sugar rose two hours after breakfast to 320 mgms.

On June 10, 1929, four days after admission the patient was given 30 units of insulin with a change of diet to carbohydrates 40, proteins 40, fat 100, making a total of 1220 calories, and yielding 73.2 grams of glucose. The blood sugar before the meal was 307 mgms. During the afternoon the patient received an additional 20 units of insulin with a repetition of the dose in one hour. During this time she complained of dryness of the throat, weakness, and pain in the legs (See Chart II, June 11).

On June 12, while the patient was still on the diet instituted the day before the blood sugar two hours after breakfast (11 A.M.) showed 330 mgms. Because of the high blood sugar findings, the patient was given 15 units of insulin at 1:50 P.M. At 2 P.M. the urine showed a trace of albumin and a trace of sugar. At 3:30 P.M. (1½ hours later) she complained of dizziness, became irrational, talkative, noisy and was tran-

siently violent and had to be restrained. The urine at this time showed albumin + + +, sugar + + + +, acetone + +, and the blood sugar was only 235 mgms.

On June 13 she was given 3 ampules of infundin at the suggestion of Dr. Evan Evans. The next morning at 2 A.M. (June 14) she became restless, talkative and dizzy. The blood sugar rose to 363 mgms without insulin (See Chart II).

The patient was placed on diets varying from a low to high carbohydrate ratio to ascertain if the blood sugar level would vary in direct proportion to the carbohydrate intake. Occasionally insulin was given to determine its effect on the blood sugar. The variations in doses of insulin administered together with the blood and urinary findings are shown in Chart I. On the day before exitus there was an acetone breath, high blood sugar. Twenty units of insulin were given on two occasions during the day. The patient became drowsy, very weak, and refused all food. There was no Kussmaul breathing and when death came, June 29, 1929, it was very sudden. There was an abrupt cessation of breathing and heartbeat indicative of vagus paralysis.

#### DIAGNOSIS

From the history of glycosuria accompanied by an increase in body weight, headache, dizziness and the fact that the symptoms of an acute infection had been present for several days, we were impressed by the fact that we were not dealing with diabetes mellitus but more likely with a hyperglycemia and glycosuria of a postencephalitic lesion in the thalamic region. The progress of the disease with the non-response to the treatment of diabetes seems to have verified our original contention. The diabetic regime and the insulin injections even in the smallest doses brought about extraordinary mental reactions. The patient became very abusive, maniacal, and

CHART II — CALORIC VALUES OF FOOD WITH DAILY FLUID INTAKE AND OUTPUT — AS WELL AS BLOOD SUGARS AND INSULIN DOSAGES

DATE	FOOD INTAKE	CARBOHY- DRATE	PROTEIN	FAT	TOTAL CAL'S	TOTAL GLUCOSE INTAKE	FLUID INTAKE	TOTAL GLUCOSE OUTPUT	SUGAR	ACETONE	DIACETIC	VOLUME IN C C 24 HRS	CARBO- HYDRATE BALANCE	BLOOD SUGAR IN A/C 100 cc	INSULIN	REMARKS
1929								Gms %								
6/6	1000 cc milk	48	32	32	608	-	-	-	+	0	0	1140	-	242	0	Dizziness
6/7	1000 cc milk	48	32	32	608	680	-	-	+++	+	0	-	-	284	-	
6/8	1000 cc milk	48	32	32	608	680	-	328 17	0	0	0	1935	-	-	-	Dizziness
6/9	1000 cc milk	48	32	32	608	680	1020	219 17	-	0	0	1290	461	-	-	Dizziness
6/10	1000 cc butter- milk & vegetable	60	36	-	440	816	1560	-	-	-	-	1920	-	320	30	
6/11	Diabetic Diet	40	40	100	1220	732	1560	-	-	-	-	1470	-	307	20-20	Dryness in Throat
6/12	Diabetic Diet	40	40	100	1220	732	1000	-	trace	-	0	1800	-	330	15-15	Irrational, Talkative, 4 hours later
6/13	24 oz milk	36	24	24	456	523	1020	448 28	trace	0	0	1600	75	363	-	Dizziness, Talkative
6/14	26 oz milk	39	26	26	494	674	2040	-	trace	0	0	1860	-	307	5	Dizziness, Restless
6/15	24 ox milk	36	24	24	456	523	2400	-	-	-	-	1200	-	123	5	Restless
6/16	Diabetic Diet	40	40	100	1220	732	2430	257 13	+	0	0	1980	175	-	10-10-5	Nervous
6/17	Diabetic Diet	40	40	100	1220	732	1830	549 10	+	0	0	5190	183	333	10-10	Irrational
6/18	Diabetic Diet	40	40	100	1220	732	2820	570 10	trace	0	0	5700	162	290	10	Restless
6/19	Diabetic Diet	40	40	100	1220	732	4860	654 10	marked	0	0	6540	78	333	-	Dryness in Throat Fair Day

6/20	Diabetic Diet	40	40	100	1220	73.2	5400	52.5	1.0	marked	0	0	5250	20.7	-	-	Intense Thirst, Drowsy
6/21	Buttermilk & Vegetables	60	36	-	440	81.6	5040	77.0	1.7	trace	0	0	4530	4.6	402	-	Fair
6/22	Buttermilk & Vegetables	60	36	-	440	81.6	5400	-	-	marked	0	0	3630?	-	333	-	-
6/23	Buttermilk & Vegetables	71	45	20	648	98.9	5400	97.4	1.7	trace	+	0	5730?	1.5	-	-	Restful
6/24	Buttermilk & Vegetables	71	45	20	648	98.9	3840	98.9	1.7	trace	+	0	5820	0	363	-	Drowsy
6/25	Buttermilk	30	19	12	308	42.0	3960	77.2	2.5	+	0	0	3090	35.2?	380	-	Sleepy, Vomiting
6/26	Buttermilk	24	16	0	160	33.0	-	-	-	+++	+	0	2040	-	333	-	Weak, Vomiting, Drowsy
6/27							3300	34.1	1.7	+	+	0	2010	-	-	-	Poor Day
6/28							3210	21.5	1.3	+++	+	0	1890	-	-	-	Vomiting
6/29										+++	+	0	-	-	374	20-25	Vomiting Restless

slapped the resident in the face so that she had to be restrained

Dr Philip Horowitz saw this case during one of the mental reactions and advised a different brand of insulin, thinking the quality of insulin might have caused the reaction. However, smaller doses of another brand caused similar violent disturbances.

During the second week of the patient's stay in the hospital, her general condition improved slightly. However, the drowsiness persisted with eventual development of stupor. The general appearance, the findings of the skin, the falling out of the hair, the dyspnea, hyperglycemia and glycosuria persisted. Towards the end vomiting was constant.

Throughout the entire time and even shortly before death there was only + acetone. Even during the agonal period when she took no food at all and vomited excessively this remained so. At no time was there diacetic or oxybutyric acid.

From an analysis of the case it appears certain that it was not one of pancreatic or insular diabetes, but that the glycosuria and hyperglycemia were of central origin. The differential diagnosis lay in whether we were dealing with a tumor or hyperfunction of the anterior pituitary or metastatic or primary tumor of the hypothalamic region or a post-encephalitic sequela in the hypothalamic region. The pituitary lesion proper was ruled out by the negative eye examination. The normal eye grounds as well as the negative neurologic signs and the normal cerebrospinal fluid ruled out primary tumor of the brain spreading to the thalamus.

region With regard to metastatic tumor in the thalamic region, we are aware of the fact that despite the negative findings, such a lesion may have been present Cases have been reported of metastatic tumor in the hypothalamic region or tuber cinereum as in a case reported by Fitcher,<sup>3</sup> without any clinical evidence of a primary tumor The complete x-ray examination of practically the whole osseous system and also of the lungs and mediastinum and the rapid course of the disease, in the case here reported, however, did not justify the suspicion of a metastatic tumor On the other hand, the sudden onset of a febrile disease, diagnosed as influenza, followed by the symptoms described seemed to us to justify the diagnosis of glycosuria and hyperglycemia of central origin following epidemic encephalitis

#### DISCUSSION

In view of the fact that pathologic lesions are not readily demonstrable in diabetes mellitus, this affection was long considered a purely functional disorder In 1855 Claude Bernard<sup>4</sup> began his search for an organic lesion to explain this important and widespread affection He punctured the medulla at the level of the origin of the vagus and auditory nerves and succeeded in producing a definite glycosuria This was brought about through the nerve fibers running to the liver by way of the hepatic plexus controlling the process of glycogenolysis As a result of this important discovery, two schools arose, one consisting of those who believed every case of diabetes mellitus due primarily to a lesion in the sugar regulating center of the

medulla oblongata (Piquère diabetes) and the other that all cases of diabetes mellitus are of psychogenic origin and that Piquère diabetes is due to psychic over-stimulation of the medulla oblongata.

Another step in the direction of demonstrating that lesions at the base of the brain may be responsible for diabetes was made in 1884 when Loeb<sup>5</sup> demonstrated that glycosuria and hyperglycemia are often associated with hyperfunction of the anterior lobe of the pituitary. Two years later Marie described a clinical entity known as acromegaly, resulted from anterior pituitary disease and frequently accompanied by hyperglycemia and glycosuria

The relation of the pituitary gland to water and carbohydrate metabolism has continued to be a subject of interest in both experimental and clinical medicine The most important and conclusive work has been furnished by Cushing and his pupils who demonstrated experimentally that hyperfunction of the anterior pituitary causes glycosuria and hyperglycemia Their work has been confirmed by many experimenters In view of the fact, however, that some experimenters have not obtained the same results as Cushing and that, clinically, in many cases of pituitary tumor or other forms of pituitary disease glycosuria is not present, and that the surgical removal in the human of the pituitary causes no disturbance in carbohydrate and water metabolism, it was natural for them to doubt the responsibility of the pituitary gland itself when diseased for disturbed carbohydrate metabolism, and to ask whether this responsibility may

not lie in the adjacent nerves or brain proper

Light has been shed on this particular problem, by Cajal and Cushing,<sup>6</sup> Clara Kary,<sup>7</sup> Elmer, Kedzierski, and Scheps,<sup>8</sup> who have shown that the internal secretion of the pituitary gland is conducted by the nerve paths from the pituitary to the midbrain and thence to the third ventricle whence it eventually enters the circulation. This internal secretion of the pituitary gland has an inhibitory influence on the insular apparatus and produces a diminished insular secretion, thus interfering with utilization of carbohydrates and leading to hyperglycemia and glycosuria. Some experimenters have shown that injury to the nerves leading from the mid-brain does not in every case affect carbohydrate metabolism.

Brugsch, Dresel and Lewy<sup>9</sup> localized with greatest exactness the carbohydrate, water and salt metabolism centers in the hypothalamic region. They located two sugar centers in the floor of the fourth ventricle. The anterior one, at the oral end of the dorsal vagus islands. Irritation of this center leads to stimulation of the pancreas with an over-production of insulin and consequent hypoglycemia, a condition clinically described by Seale Harris,<sup>10</sup> and pathologically demonstrated by Wilder,<sup>11</sup> to be produced by adenoma of the islands of Langerhans.

Brugsch, Dresel and Lewy have shown that extirpation of the pancreas leads to secondary degeneration of the oral end of the dorsal vagus nucleus (anterior sugar center). These authors have shown a second sugar center, a caudal one, at the posterior end of the dorsal vagus nucleus. This is a

sympathetic center sending its fibers by way of the jugular ganglion of the vagus and superior cervical sympathetic ganglion affecting the blood sugar level by way of the suprarenal glands. Irritation of the posterior sugar center leads to stimulation of the suprarenal glands with resulting hyperglycemia.

The work of these authors clearly and satisfactorily explains the experimental Piqure diabetes of Claude Bernard, as well as the occurrence of glycosuria in some cases of apoplexy, basal meningitis, tumors of the base of the brain, metastatic tumors especially in the hypothalamic region, and the not infrequent disturbance of water, salt, carbohydrate and thermic metabolism encountered as sequelae of epidemic encephalitis.

The work of Brugsch, Dresel and Lewy has been verified by many experimenters and some clinicians, notably among them Eric Leschke.<sup>12</sup> Leschke goes so far as to attribute the disturbance in carbohydrate metabolism solely to a central origin, contending that all cases of diabetes mellitus are due to a functional or organic disturbance in the hypothalamic region, and that any co-existing lesion in the islands of Langerhans is merely secondary. In the vast number of cases according to Leschke an actual lesion of a carbohydrate center need not be present. A functional disturbance alone may suffice to inhibit the action of the islands of Langerhans by way of the sympathetic and thus bring about hyperglycemia and glycosuria. Just as L. Pick<sup>13</sup> of Vienna and H. Elynn<sup>14</sup> of New York adhere to the conviction that salt and water metabolism dis-

turbances are entirely under the influence of the hypothalamic region, so is this claimed by Leschke for carbohydrate metabolism disturbance.

Enlightening as the results of the experiments of Brugsch, Dresel and Lewy, may have been, the recent work of Hiller and Tannenbaum<sup>15</sup> as well as of Hiller and Grinker<sup>16</sup> has cast great doubt upon those results. Hiller, Tannenbaum and Grinker have come to the conclusion that the carbohydrate disturbance brought about by the Brugsch-Dresel-Lewy experiments is not due to an actual hypothalamic lesion, but to certain technical errors in experimentation and in the interpretation of the experiments. They have shown that even ether anesthesia or manipulation of the head of an animal without causing a lesion in the hypothalamic region brings about glycosuria in the animal. They are skeptical as to whether any of the centers such as the salt and water centers are present in that location.

It is quite apparent that in most branches of medical investigation, especially regarding metabolism, the clinician must not be too much influenced by the results of contradictory experiments, else he cannot hope to escape confusion. It seems pretentious for one who himself has not partaken in the experiments to side conclusively with one or the other faction. The position of the clinician should, after all, be determined by clinical observation in a matter of contradictory experimental evidence. Clinically, it cannot be denied that cerebral lesions particularly those confined to the hypothalamic region, the pituitary proper and the connecting nerves between the

pituitary and hypothalamic region, do give rise to disturbance in carbohydrate, water and salt metabolism. This was so well known long before the experimental era that it would mark a considerable step backward in clinical interpretation if one were to deny it simply on the basis of a recent contradictory experiment, no matter how authoritative the source of that experiment might be. It would be just as fallacious, however, if influenced by the experimental work demonstrating a metabolic center in the brain, one were to conclude that disturbance in carbohydrate, water and salt metabolism must in every case be traced to functional disturbance or to a pathologic lesion in the pituitary or in the hypothalamic region.

It is our opinion that every affection—organic or functional—and this concerns disturbances in metabolism more than any other disease, may originate either in the central nervous system, particularly in the vegetative centers, or in an organ proper. Regarding disturbance in carbohydrate metabolism, there is no doubt that purely functional disturbance of a non-progressive nature can and often does originate in the central nervous system or in a dysfunction of the thyroid or suprarenals. This form of carbohydrate disturbance is not synonymous with diabetes mellitus due to a disturbance of the islands of Langerhans. In reality, they are two independent affections.

In a state of health, the two centers—one central, the other peripheral—have an antagonistic activity. The posterior end of the dorsal vagus nucleus in the thalamic region stimulates the suprarenals causing a hyperglycemia

and equalizing the possible hyperglycemia from insular overproduction by the anterior center. If this equalization does not occur spontaneously, the administration of adrenalin brings it about. This is illustrated by the fact that hyperglycemia resulting from adenoma of the pancreas (Wilder) or hypofunction of the suprarenals (Addison's disease) is at least temporarily favorably influenced by adrenalin.

A co-affection of several organs concerned in the same process of metabolism, such as can be brought about by animal experimentation, is unlikely in the human unless chance or accident causes a rapidly destructive disease of one of these organs so that no time is given to the affected organ or to the organs with compensatory mechanism to adapt themselves to the situation. It is true that thyrotoxicosis, hyperadrenalemia and hyperfunction of the anterior pituitary lobe can produce glycosuria. However, in order for affection of these organs to lead to a permanent or true diabetes indicating that a co-affection of the islands of Langerhans is present to a degree that a diminished amount of insulin, or insulin of a less effective nature, is produced, rapidly destructive thyrogenic or suprarenal disease must be present, conditions only rarely encountered clinically. This is even more so in case of a hypothalamic lesion causing hyperglycemia and glycosuria. It is equally important to remember that a rapidly destructive disease of the islands of Langerhans such as is brought about by a cyst of the pancreas or syphilis of the pancreas may progress so rapidly as to affect the carbohydrate center in the thalamic region. The antagon-

istic functional activity of the hypothalamic region can not keep pace with the rapidly destructive process in the islands.

The clinical proof that glycosurias of non-insular origin not only co-affect the islands but most likely stimulate them to increased insulin secretion is demonstrated by the fact that glycosuria of hyperadrenalemia or hyperthyroidism or of functional or organic thalamic lesions are in most cases transient. But even if they persist—as in the case herein reported—neither the hyperglycemia nor glycosuria is aggravated by the additional intake of carbohydrates, nor is there a favorable influence exercised on the carbohydrate metabolism by the administration of insulin. Actually, as in our case again, insulin may be harmful. The patient has enough insulin so that the additional exogenous introduction serves as a definite stimulant to the insulin output and hyperinsulinemia results. Even where insulin is not directly harmful, the individual is refractory to it.

Clinical substantiation of the statement that disturbance of carbohydrate metabolism resulting from insular disturbance differs entirely from that of the extra-insular apparatus (hypothalamic, thyrogenous, suprarenal) is further provided by the fact that in the former the administration of carbohydrates fails to bring about an equal response of the islands in the output of insulin. Hence marked hyperglycemia and glycosuria occur. In "extra-insular" carbohydrate metabolism disturbance, the administration of carbohydrates stimulates, just as in the normal individual the insular apparatus to additional insula output. Con-



sequently there is no increase in the blood sugar and at most only a very slight increase in glycosuria. This is true, also, if the glycogenic function of the liver is disturbed and the liver does not store the glycogen either as a result of some inherent disease in the liver (hepatogenous glycosuria) or as a result of a disturbance in the thalamic center or suprarenals by way of the sympathicus. The excess of sugar in the blood stimulates the insulin apparatus to increased insulin output of effective quality so that the consequences of hyperglycemia or glycosuria, namely acidosis or diabetic coma, do not occur.

Von Noorden and Isaac<sup>17</sup> have described a form of glycosuria due to the excessive deposit of fat in the liver. Because of this excessive fat in the liver, it is impossible for glycogen to be deposited there. Hence the excess of sugar that is not deposited as glycogen passes out through the kidneys. These cases have no hyperglycemia unless very large quantities of carbohydrates are taken. Even then the hyperglycemia is only transient. Because of the lack of assimilation of the intake of carbohydrates the patient grows gradually weaker, although appearing strong. When disturbance in fat metabolism also sets in the patient becomes slowly acidotic, develops small quantities of acetone in the urine and becomes drowsy. This form of glycosuria differs from diabetes in those fat individuals where there is an excess of fat in the pancreas replacing the islands of Langerhans and thereby interfering with the output of insulin.

From what has been said, it seems almost paradoxical to group all cases

of glycosuria and hyperglycemia as diabetes, or to insist that if one center of a cycle controlling metabolism is disturbed the others are necessarily co-affected. The reverse, in fact, is the case. If one center of carbohydrate metabolism is affected, the others come to the rescue in their accommodation as a compensatory mechanism. *We feel that an existing glycosuria and hyperglycemia indicate true diabetes mellitus only if the insular apparatus of the pancreas is defective.*

Should the affection lie in the thalamic center alone, or in the organs of internal secretion (thyroid, suprarenals or pituitary) the glycosuria and hyperglycemia are of the neurogenic type resulting from the sympathetic influence on the glycogenic function of the liver, in which case the islands of Langerhans are not—as stated by some authors—inhibited, but, in our opinion, are stimulated to greater insulin output in order to utilize the excess of carbohydrates and prevent acidosis.

In other words, the “extra-insular” carbohydrate metabolism by virtue of the endogenous excess of carbohydrates stimulates the insular apparatus to the production of insulin just as does an exogenous carbohydrate intake. Of course, it may be readily assumed that if such an endogenous carbohydrate excess exists—whether the cause be in the pituitary, thalamic center, liver, thyroid or suprarenals—it may exhaust the islands of Langerhans and even lead to their destruction and result in acidosis. It is possible, too, that in some cases of complete destruction of the islands of Langerhans, as may happen in a rapidly progressing pancreatic cyst or in syphilis

of the pancreas, over-stimulation of the compensatory centers may eventually lead to irritation and even to destruction of these centers, as is sometimes demonstrated in the acute animal experiment. This is clinically the exception.

#### CONCLUSIONS

A clinical case of extra-insular (central) hyperglycemia and glycosuria has been described. An effort has been made in both the description of the case and in the discussion not to confuse diabetes mellitus due to affection of the islands of Langerhans with hyperglycemia and glycosuria of extra-insular origin, be that origin central, thyrogenic, or suprarenal.

It is confusing to divide diabetes mellitus into insular and "extra-insular" groups. True diabetes is always insular. The "extra-insular" type spoken of by Umber,<sup>18</sup> which is refractory to insulin, is not true diabetes, but should be termed "extra-insular" glycosuria with or without hyperglycemia. In the insular type of diabetes, insulin exerts a favorable influence and in some cases the function of the islands can be entirely restored by its protracted use so that complete recovery results. It is well known and has again recently been further confirmed that in most cases of diabetes mellitus there are no demonstrable pathologic changes in the islands and that the disturbance is of a purely functional nature. The administration of insulin, therefore, spares the insular function and gives the islands a chance to recuperate and eventually return to normal.

In extra-insular glycosuria and hyperglycemia, on the other hand, the administration of insulin causes an in-

creased output of endogenous insulin with the immediate effect of hyperinsulemia, which cannot be favorably influenced by the administration of carbohydrates or of adrenalin. The reason for this is that in insular diabetes the administration of carbohydrates or even of adrenalin does not bring about an extra production of insulin and hence the carbohydrates actually counteract the insulin shock. In extra-insular hyperglycemia or glycosuria, however, carbohydrates or adrenalin cause a greater output of insulin by the islands of Langerhans and are, therefore, harmful.

The administration of even the smallest doses of insulin in cases of extra-insular glycosuria, with or without hyperglycemia, especially originating in a disturbance in the pituitary or hypothalamic center, produces—as in our case—a violent mental reaction that is unlike the temporary manifestations of hyperinsulemia in insular diabetes, namely, marked weakness, cold perspiration and collapse manifestations, immediately relieved by the administration of carbohydrates or adrenalin.

There are, of course, cases of extra-insular hyperglycemia and glycosuria that behave very much like insular diabetes, terminating in acidosis. They are probably either complicated cases, or the central lesion may have been so severe and so rapidly destructive as to have actually led to secondary changes in the islands of Langerhans.

Many characteristics differentiate insular diabetes from extra-insular glycosuria with or without hyperglycemia. In addition to those already enumerated, it is important to remember that

true insular diabetes causes not only a disturbance in carbohydrate metabolism, but also a disturbance of fat and protein metabolism. This is not the case in extra-insular glycosuria with or without hyperglycemia

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# Obesity

## Observations on Treatment by Dietary Measures

By D N KREMER, *Philadelphia, Penn*

THE excessive deposition of fat in the body, either as a result of overnutrition, or a disturbance of the glands of internal secretion, is quite a common occurrence clinically. Obesity may be divided etiologically into two types, not always clearly defined—the exogenous and endogenous varieties. In the exogenous group are included those cases in which the only discoverable cause may be attributed to race, heritage or habits of life. The tendency toward a gradual increase in the general deposition of fat during and after middle life, is largely dependent on changes in habits. Over indulgence and ignorance as to the need of curbing the appetite, with the associated decrease in physical activity, and lessened energy requirement, is a contributing factor in the development of obesity. Exercise is likely to be reduced, and material success, with its associated abundance of good food, favors fat storage in the body. Especially is this true in the male of the species. Corpulency in women is much more common, and apparently less influenced by habits. The periodicity of sex function in women, seems to have a greater influence on fat deposition than is the case in men. After the climacteric, there is commonly a marked tendency to corpulency. Opposed to

these general tendencies, are those individuals who retain a constant weight within wide limits of food ingestion.

Newburgh and Johnston insist that obesity is always caused by an overabundant inflow of energy. The excess is deposited as adipose tissue. Body weight is the resultant of two factors, either a gain or loss of tissue, or a gain or loss of water. The loss of one and a gain in the other may neutralize each other; or a large retention of water may cause a gain in weight, even though body tissue has been consumed, and may lead one to draw erroneous conclusions, if there is a failure to take water exchange into consideration. The response of various types of obese people, does not differ from that of normal people. All of them oxidize body tissue in accord with the prediction from the caloric deficit. Retention of water may proceed for several days, or loss of water may be suddenly precipitated.

Wm E. Preble in an analysis of one thousand cases, came to the conclusion that obesity is almost invariably due to bad dietary habits, and not to hereditary errors in metabolism. Strouse and others have found, that there is a constitutional tendency to obesity. While the food intake may not be great, the tendency to obesity is great. The basal

metabolism in the obese is usually within normal limits. Their interesting contribution is that the specific dynamic effect of proteins is much less in the obese than in the thin individuals. The same is true for carbohydrates. They also found that during a state of fatigue, in the normal individual the heat production is slightly increased, and the mechanical efficiency is lessened. When obese individuals are compared with normals, the heat production is much greater, and the mechanical efficiency is much less, also, fatigue came sooner in the obese, than in the undernourished.

B. D. Bowen has shown that the vital capacity in obese and overweight individuals is but slightly less than normal. The tendency to dyspnea in the obese may be accounted for, in part at least, by a reduction in vital capacity. The weight of obese subjects should be reduced slowly, especially if there is dyspnea, as a definite reduction in vital capacity occurs with the development of symptoms of a cardiac nature.

Hagedorn and others have found that the respiratory quotients in obese persons are lower than in normal individuals. Their results confirm the hypothesis that obesity is due to a qualitative anomaly in metabolism, i. e. an abnormal increased transformation of carbohydrates into fat. It has been shown that a relation exists between the percentage overweight and the respiratory quotient in obese subjects. Patients with great overweight have a particularly low respiratory quotient, while those with less overweight, have a respiratory quotient which is nearer or within the normal zone.

Goldblatt, in his study of sixty cases of exogenous obesity, found, that there is no impairment in the oxidation of carbohydrates, but a delayed storage. This reduction in the storage power was considered to be secondary to the obese condition. No abnormalities of carbohydrate metabolism were discovered in one hundred adolescents with endogenous obesity.

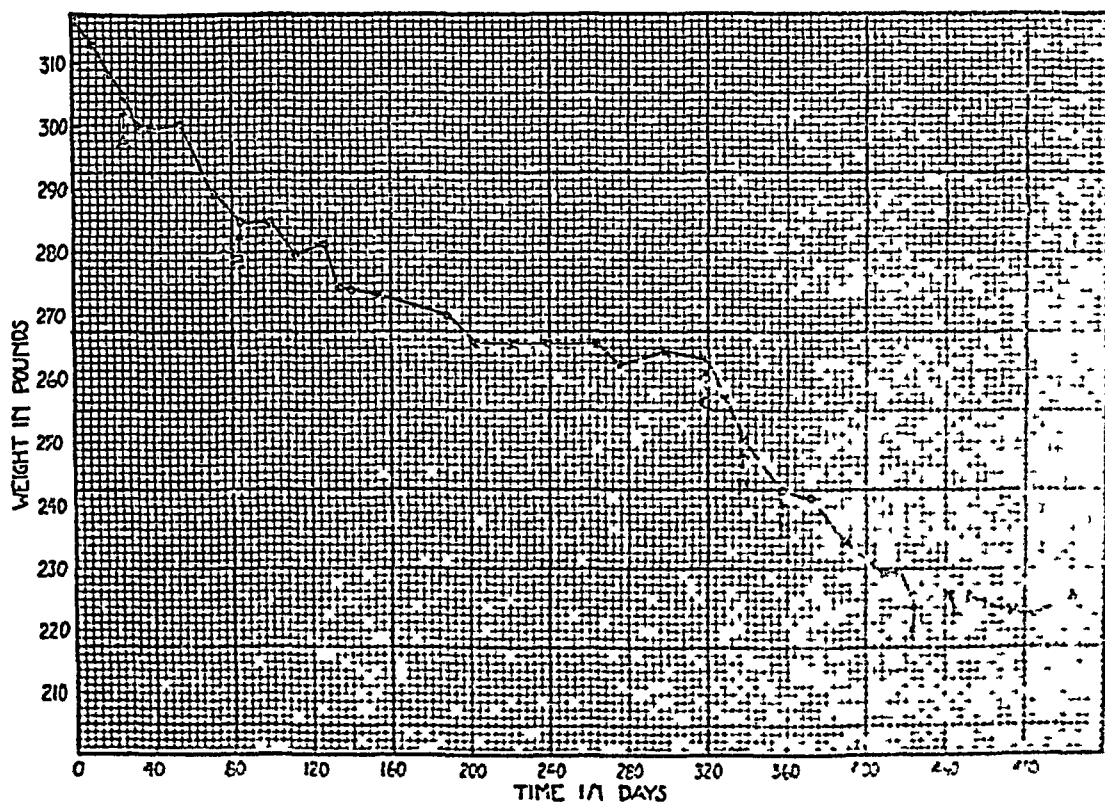
The endogenous or constitutional group of obesities comprises those cases in which there is more or less well-defined pathological etiology. From the glands of internal secretion, may be sought the cause of a certain number of these obesities. Castration in either sex is followed by an increase in weight and frequently associated with marked obesity. The tendency to stoutness, subsequent to the menopause, may be included in this category. Tumor of, or in the neighborhood of, the pituitary gland, may lead to extraordinary degrees of adiposity, associated with sexual infantilism (Frohlich's Syndrome). This condition is found most frequently in children and young adults. Removal of the posterior lobe of the pituitary gland is followed by a great increase in weight, due principally to the general deposition of fat. Perverted functional activity of the pituitary gland, usually spoken of as hypopituitarism, or hypophysectomy (dystrophia adiposogenitalis) may be another cause. Abnormal function of the thyroid, or hypothyroidism, with or without the symptom complex, known as myxedema, may be responsible for large increases in adipose tissue, and the term thyrogenic obesity applied. Any lessening in the basal metabolic rate for

any reason, favors the development of obesity

Basal metabolism in the endogenous cases has been found to be low, varying from 25% to 50% below normal. In these instances there is no evidence that the fat metabolism is abnormal, but merely that metabolism is less intense. The body requirement is less. Associated with the obesities, due to derangements in the functions of the glands of internal secretion, there are frequently subnormal temperature and a low nervous tension, factors which influence the amount of heat produced

Combined with a low energy requirement, the sluggish habits so commonly found in these cases, and a liberal food intake, the resultant fat increase in the body is a perfectly normal process. Associated with this there is a disturbance of water and salt balance in addition to faulty metabolism.

The general impression that in exogenous obesity the basal metabolic rate is normal, receives additional confirmation in a study made by Topper and Mulier on 35 boys and 35 girls, between the ages of 6 to 14 years, using the Pirquet Standards.



EXPLANATION OF CHART 21 Case of P.P.

Patient's weight at beginning was 316½ pounds

At point A, began the use of moderate doses (6 grains daily) of thyroid gland extract. Point B Thyroid therapy stopped, because of reaction, and diet alone continued. At C, again started on thyroid therapy. At D thyroid was reduced to 30 grains a day, because of slight complaint of nervousness. At E, thyroid dose again increased to 60 grains a day, with weekly injections of Aolin. At F, Thyroid and Aolin stopped and continued on diet alone.

Recht found that obese individuals absorb saline more rapidly than normal individuals. There were, however, marked regional differences, which were not altered by copious drinking of water, or the administration of pituitrin. The administration of pituitrin revealed the existence of a marked antidiuretic action in some cases of obesity. In contrast to this Hunt found in his cases that the limitation of diet, in the so-called constitutional obese, was of no avail, and that subcutaneous injections of 1 cc of pituitary preparations for two weeks, were useless.

In an attempt to determine just what may be accomplished with the average obese patient that one meets in an outpatient clinic, or in general practice, and what improvement occurs in their general condition, upon a reduction in their weight, this study was undertaken. Those of us who are connected with an outpatient clinic of a large hospital, are constantly impressed by the association of overweight with definite physical complaints on part of the patient. The series of cases studied were not selected because of any special factor in their obesity, but represent patients who came to the medical clinic of the University Hospital for various other complaints. None of them was sufficiently disturbed by their overweight to mention it as their chief complaint. The cases analyzed are those which came under our observation within a definite period of time.

In beginning our dietary management, we realized that the underlying principles of all reduction were the maintenance of nitrogen equilibrium, and at the same time keeping the carbohydrate and fat ingestion at such a

level that the total food intake is below the daily requirement, with the consequent result that body fat is called upon to make up the deficiency. We desired to establish a gradual loss of weight, and in this way maintain a sense of well being on the part of the patient, with a greater likelihood of continued adherence to diet.

A well balanced diet is essential for a low caloric intake. Such a diet must provide a variety of food, which will furnish in abundance the protein needed for muscle building and repair, the necessary fuel needed for energy, and regulating food containing vitamins and minerals, which influence all body processes and increases resistance to disease.

A reducing diet should be planned on the total fuel value of the diet for a normal individual, being based on the average height, weight, age, sex and occupation.

We realized that any plan of dietary restriction instituted was not under strict control as to dietary adherence.

In order to be assured that the factor of error in our observations should be minimized, we did not follow the plan of Grafe, by restricting the caloric intake in proportion to the excessive weight of the patient. For the same reason, we did not make any effort to control the salt intake. Knowing the average run of patients seen in a medical clinic, the dietary management advocated by Evans and Strong would be subject to criticism, as there is an ever present possibility of the patients studied, adding snacks to their diet, which, to them, appears to be of little importance, but appreciably increases their caloric intake.

By a more liberal caloric diet, we felt that greater adherence to their regime was possible, and better cooperation on part of the patient. One could also figure their caloric intake as being more accurate.

All the patients were placed on a diet of approximately 1400 calories, as such a diet will allow a gradual loss of weight. The protein was calculated to be about 13 gm per kilo of body weight. This insured the patients against using their own protein, consequently little or no weakness was felt during the period of dieting. The carbohydrate approximated 200 grams, and with this amount danger of acidosis was lessened. A sufficient quantity of carbohydrate was given in the form of 5% and 10% vegetables to satisfy the patients' appetite. No free fat was given. The amount of fat in the diet was combined with the food in the form of egg, cheese, meat, etc. In addition sufficient vitamins and minerals were provided to prevent any possibility of malnutrition developing.

With this diet, weight was not lost too rapidly, nor did it interfere with the patient's routine of life.

The cases were instructed to report weekly for observation, and at each visit a check-up on their diet was made by the dietitian. In spite of this we found it difficult, in all the cases, to maintain a strict adherence to the diet, over a long period of time. Allowing for occasional lapses, we felt that those patients in whom definite weight loss occurred had adhered closely to their outlined regime. In those patients in whom we failed to obtain any evidences of weight loss, after several weeks, we obtained a confession from

them that they had lapsed in following their instructions. Often in such instances, following a lecture on the importance of cooperation on their part, there occurred a subsequent loss in weight. No attempt was made to advise exercise, because of the difficulty in standardizing and checking such measures.

As all our cases were women in whom there was not much likelihood of a change in their general routine and habits of life, we can safely assume that the question of physical activity was not an important factor in their reduction of weight.

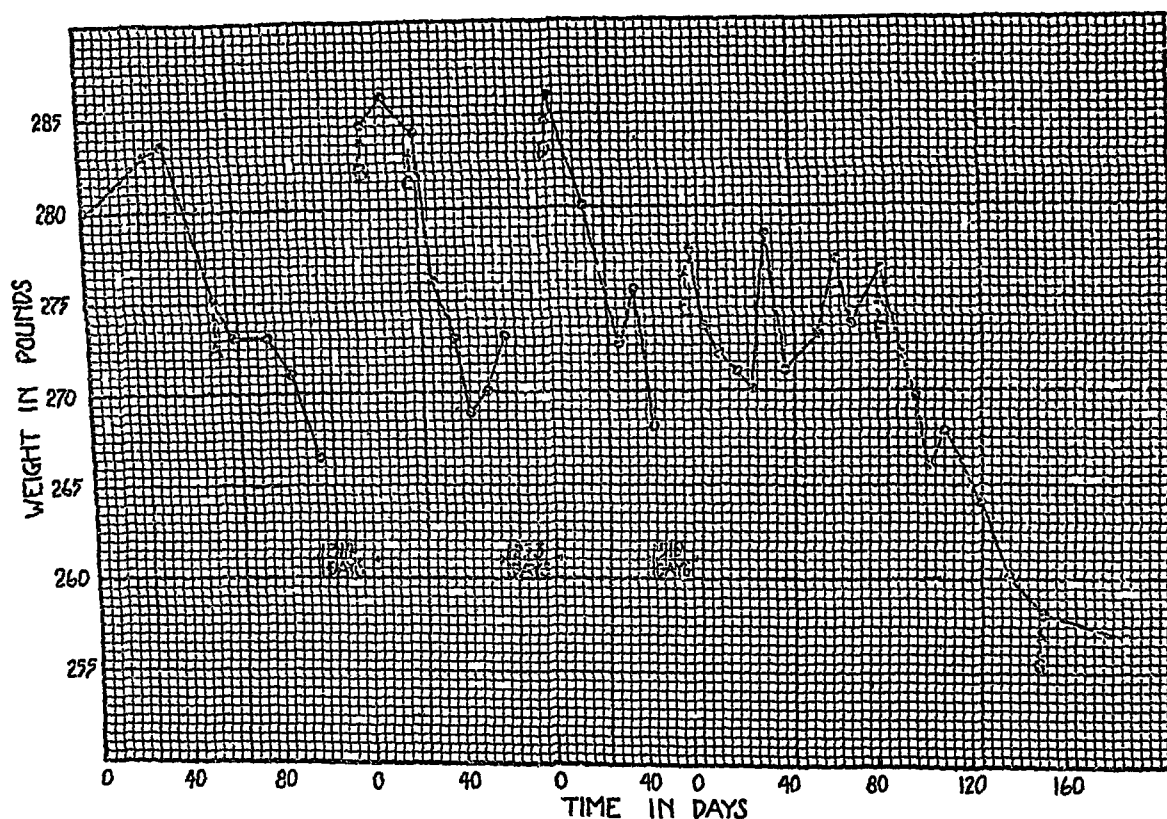
The total number of cases studied was fourteen, and they were kept under observation for a period varying from three to eighteen months. One of these cases showed a definite evidence of glandular disturbance—a thyro-pituitary type, with a basal metabolism of -12,—and this case we did not include in our study. We confined ourselves to those obese individuals, who, as far as we could determine, came under the exogenous classification. The basal metabolism in all these cases were within normal limits. The highest was +18 and the lowest +5. They were all women who were married, and gave a history of having one or more children. Their ages varied. One case was 25 years old, five were between 30 and 40 years, six were between 40 and 50 years, and two were 54 years. One of the patients had definitely passed her climacteric, while in another in whom we succeeded in obtaining a marked reduction in there occurred a return of menstrual flow, after a lapse. Two of the cases, who



ginning of our study, were going through the climacteric, during the period of observation, had a normal restoration of their menstrual flow.

As a group, their chief complaints were mainly those of back pains, joint symptoms, dyspnea on exertion, gastric distress and nervousness. In one of our cases there was a definite history of gall bladder disease, and in

two others the physical findings were indicative of myocardial involvement. One case, the only complaint was that of a *Taenia saginata* infestation, and upon cure of this condition the patient failed to return for further observation. One of the cases, with definite myocardial disease, was referred to us from the eye clinic because of an optic neuritis, and coincident with her re-



EXPLANATION OF CHART #II—*Case of L. B.*

First curve represents patient on diet alone. A primary increase in weight noticed, instead of a decrease. Following a lecture to the patient, with insistence upon strict adherence to the diet, there is a marked drop. At A, Thyroid in moderate doses was given, with continued loss in weight.

B represents the weight of the same patient after a lapse of 314 days, with no dietary regime. Again placed on a diet. At C, Thyroid started in conjunction with the diet. D represents weight of same patient after a lapse of 253 days. This time immediately placed on diet, plus thyroid therapy. At E, patient returned after a lapse of 519 days. At this time we had undertaken a detailed study of our obese patients, hence we lectured her on the desirability of co-operating with us, and continuing under our constant observation. She was placed on diet, plus thyroid, with periods in which diet alone was used. The increased loss of weight occurred at time of thyroid therapy. At point F, after a period of diet alone, patient was placed on increased thyroid dosage (nine grains daily) with weekly injections of Aolan. At G Thyroid and Aolan discontinued.

duction in weight, there occurred a disappearance of her optic neuritis. There was also one case which presented definite evidence of focal infection, with tonsils that were diseased and from which pus could be expressed, and in this instance, reduction in weight failed to bring about any improvement in symptoms.

An interesting observation noted was the effect upon the blood pressure readings following a definite reduction in weight. The blood pressure readings in this series ranged as follows: In 10 cases it varied between 110 and 150 mm Hg. Between 175 and 200 in three cases, and above 200 in one case. In the one patient whose blood pressure was above 200 at the beginning of our study, we were able to show a reduction of 60 mm Hg. In the three cases which were between 175 and 200, we obtained an average reduction of 40 mm Hg.

In a paper published by Masters and Oppenheimer, subsequent to our study, they clearly demonstrated the general improvement in symptoms evinced by obese cases, especially in circulatory and cardiac cases. They found a drop in blood pressure, reduction in pulse rate and general improvement in cardiac function, shown by roentgenogram and electrocardiogram, also a distinct increase in the patient's exercise tolerance, with the reduction in weight.

In the dietary management of our cases, we failed to obtain any loss of weight in three patients, because of lack of co-operation on their part, and the results obtained were negative in character. Four were kept on diet alone and by this measure alone we

were able to maintain an average loss of weight, varying from one to three pounds per week, depending upon degree of co-operation. Two cases, in whom there was observed a desire to co-operate, were placed on mild doses of dried thyroid gland substance, averaging six grains a day and there was noticed an additional loss of weight of approximately a pound a week. In five cases we kept the patient on a diet, and because we reached an impasse in their weight loss, we placed them on thyroid therapy, and found that the average period before one could expect a reaction to the thyroid therapy varied from four to six weeks. After that time they began to complain of nervousness and cardiac palpitation. In these cases we then started them on weekly injection of 5 cc of aolan, in accordance with the findings of Julius Bauer of Vienna, who observed that he could continue the use of thyroid for a much longer period without reaction occurring, by the coincident use of a non-specific foreign protein. In our five cases we also found that thyroid therapy could be continued, after thyroid reactions were observed, for an extra period of time, varying from five to eight weeks. In two of these cases we increased the daily dosage of thyroid from six to nine grains per day, and we were consequently able to obtain a greater reduction in weight and thyroid symptoms did not develop until after a month of active treatment. Our criterion of thyroid reaction was objective evidence, such as rapid pulse or tremors, or subjective complaints on part of the patient, such as nervousness or cardiac palpitation.

In the cases studied, where dietary measures were successful, there occurred a definite loss of weight in ten of the cases. The aggregate loss was 385 pounds. The shortest period of observation was three months in one case, with a loss of eleven pounds, and the greatest single loss was 93½ pounds in a period of sixteen months

### CONCLUSIONS

1. In cases of obesity, an adherence to a prescribed diet, as outlined, will bring about an amelioration in symptoms, a definite lowering of blood pressure, when it is high, and a general improvement in the patient's physical condition.

2 Average loss of weight depends upon length of observation, and degree of continued adherence to a diet.

3 Strict adherence to a balanced diet will bring a gradual loss of weight, varying from one to three pounds per week, up to a certain point, depending

upon degree of co-operation on part of the patient.

4 Moderate doses of thyroid therapy, plus diet, will cause an extra loss of weight, averaging one pound a week, and one can usually continue thyroid therapy from four to six weeks before evidence of thyroid reaction occurs

5. The moderate use of thyroid therapy, without adherence to a diet, fails to cause an appreciable loss of weight

6 Aolan injections, plus thyroid therapy, give one an opportunity for greater dosage of thyroid, with an increased loss of weight, and a prolongation of the period of time before reaction occurs.

7 In patients where an adherence to a diet is difficult to maintain, a course of thyroid therapy, with weekly injections of 5 c.c. of aolan, will help to bring a reduction of weight sufficient to encourage the patient. This will prove beneficial in bringing about further dietary adherence.

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# Chlorotic Anemia with Achlorhydria, Splenomegaly, and Small Corpuscular Diameters\*

By WILLIAM S. McCANN, M. D., and JANE DYE, A. B.,  
*Rochester, New York*

THE brilliant specific results of liver therapy in pernicious anemia announced by Minot and Murphy<sup>4</sup>, following upon the demonstration by Whipple and Robschert-Robbins<sup>8</sup> of the importance of liver feeding in the chronic anemias of dogs, induced by repeated bleeding, have led to a widespread attempt to treat all anemias with liver. In many of the so-called secondary anemias the response to liver therapy is only partially successful and in others entirely disappointing, when compared with the results in pernicious anemia.

It is the object of this paper to present the clinical features of a group of anemic patients, all of whom failed to derive benefit from liver therapy, all of whom responded as promptly and specifically to massive doses of iron as pernicious anemia responds to liver. From the standpoint of hematological criteria the anemia here described is differentiated from pernicious anemia by its low color index, red corpuscles the average size of which is below normal, without bilirubinemia; which is in

sharp contrast to the high color index, macrocytosis, and bilirubinemia of the latter. It shares achlorhydria as a common characteristic with pernicious anemia, and, like the latter, has a tendency to recur.

In 1913 Knud Faber called attention to the association of achylia gastrica with simple anemias of chlorotic type as well as with pernicious anemia. In 1924 he published with H. C. Gram<sup>1</sup> further observations. Of 63 patients with uncomplicated achylia, 36.5 per cent were anemic. In the patients with normal hemoglobin the color index fluctuated about 1, while the index in the anemic cases was nearly always decreased. In the more pronounced cases the small size of red corpuscles was clearly visible in the stained films. The anemia was distinctly more frequent in women than in men and most of the severe cases occurred among the former. Megalocytes and megaloblasts were never observed. Stippling and reticulation were observed only during treatment with large doses of iron and never in untreated cases. The leucocytes were either normal in number or slightly low. Faber and Gram did not give detailed case reports of the clinical features of this achylic chlor-anemia. They state that it is of a

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\*From the Department of Medicine of the University of Rochester, School of Medicine and Dentistry, and the Medical Clinic of the Strong Memorial Hospital, Rochester, N. Y.

rather benign character, not lethal, but refractory toward treatment, and that it tends to recur. It occurs in both sexes and at all ages. No tendency to spontaneous or permanent recovery was noticed. The most successful treatment was with massive doses of iron.

More recently, Kaznelson, Reimann and Weiner<sup>8</sup> have given detailed case reports of patients with an "achylic chloranemia." Their patients presented themselves with a variety of complaints, chiefly those due to the anemia, such as palpitation, weakness and pallor, though many patients came under observation because of gastro-intestinal symptoms, such as diarrhea associated with achylia. Their patients were of all ages and of both sexes. Females predominated slightly. Among their patients splenomegaly was not a frequent finding. Some of their patients had a Hunterian glossitis, and papillary atrophy, and some had paresthesias suggestive of a disorder of the posterior columns of the spinal cord. Some patients had a koilonychia of both hands and feet. The blood changes were described as follows: anemia with low color index, without leucocytosis, sometimes with a slight lymphocytosis and normal platelets. The serum was colorless and showed no increase in bilirubin, or other evidences of heightened blood destruction. Urobilinogen was found in the urine only in traces. Evidence of occult bleeding was absent. As to therapy, these authors found that liver was wholly inactive, and they regarded iron as a specific for achylic chloranemias.

An important finding is reported by Weiner and Kaznelson<sup>8</sup>, who studied the marrow obtained by sternal punc-

ture, before and after treatment. They found an excessive increase in erythroblasts, which in all cases were exclusively normoblasts, 30-47 per cent of the marrow cells as compared with the normal 20 per cent. Megaloblasts were never found. Two punctures of the sternum following successful treatment revealed normoblasts in normal proportions.

The discrepancy between the chronic anemia and the richness of the bone marrow in erythroblasts, without evidences of increased hemolysis or blood loss, was very striking. The inference was drawn that there was a disturbance in the maturation of the erythroblasts in the bone marrow. After administration of iron they noted a rapid increase in erythrocytes taking vital stains (reticulocytes).

Most descriptions of true chlorosis mention small diameter of red cells as a matter of diagnostic importance. Minot<sup>5</sup> states that "with improvement, increase in the number of red cells, often to normal or above, occurs long before the cells regain their size or proper complement of hemoglobin."

In connection with the cases to be reported here we chose the method of Price-Jones<sup>7</sup>, to secure data upon the average diameters of the red corpuscles in chlorotic anemias. The frequency of distribution of corpuscular diameters was determined by measurement of 300 corpuscles in freshly dried smears, fixed and stained with Wright's stain, using an ocular micrometer. The results obtained were subjected to analysis according to the recommendations of Pearl<sup>6</sup> to determine the significance of the differences in mean diameters

found in relationship to the probable errors of the means.

The ocular micrometer disc was ruled to 5 mm in 0.05 mm divisions, with every twentieth line numbered. With an oil immersion lens (97x), a number 10 ocular and a tube length of 160 mm, each line measured 0.869  $\mu$ . Cells falling on the ruled space were measured as 40, 45, 50, 55, etc., lines in diameter. Measurements were made on smears taken as nearly as possible under the same conditions and at the same time of day in each case. Hemoglobin was determined in a hemoglobinometer of the Sahli type with a permanent glass standard. Each diluting tube was calibrated with a standard hematin solution made from blood whose oxygen capacity was accurately determined by the method of Van Slyke and Neill<sup>12</sup>. Forty minutes were allowed for the development of the color of acid hematin. Red cell counts were made with certified counting chamber and pipettes. The color indices were calculated on the basis of a correspondence of 5 million corpuscles and 100 per cent hemoglobin equal to 150 grams per 100 cc of blood.

#### CASE REPORTS

*Case I No 3771.* A married woman 35 years old was first seen November 4, 1926, for the complaint of perpetual fatigue and pallor. These symptoms dated from early childhood. Anemia became marked and was accompanied by a nervous breakdown while she was in college. She married at 26 and gave birth to three normal children in 9 years. In each pregnancy she was quite anemic. After the last pregnancy in the spring of 1925 her hemoglobin was 45 per cent. Aside from the exacerbations of fatigue and pallor there were unusually few specific illnesses. There had been no unusual blood loss, no peculiar pigmentation or jaundice.

The catamena began at 13 years and was quite normal. The pregnancies were marked by rather prolonged vomiting and by pressure symptoms. The first two labors were induced after term but were otherwise not unusual.

The examination revealed a normally developed and well nourished woman, with marked pallor, no jaundice, nor abnormal pigmentation. There was no general or regional enlargement of lymph nodes and no evidence of purpura. The tongue revealed no papillary atrophy. There was a soft systolic murmur heard over the apex of the heart, which was otherwise normal. The spleen was *palpable* just below the costal margin. The liver edge could be felt 2 cm below the costal margin in the mid-clavicular line. The blood pressure was 124 mm of Hg systolic, 78 diastolic. There was a moderate endocervicitis, but no other pelvic abnormality. The neurological examination was normal throughout. Vibration was well perceived. The urine was normal on several examinations and the phenolsulphonephthalein test of renal function showed normal dye excretion.

The blood Wassermann test gave a weak positive reaction with the cholesterinized antigen and the Kahn precipitation test was ++.

Two gastric analyses were done, which showed an absence of free hydrochloric acid in the fasting contents and after an Ewald meal, with very low total acidity.

The peculiar feature of the blood examination was an *anemia with a low color index*.

On November 4, 1926, the blood examination was as follows: hemoglobin 58 per cent ( $100\% = 15$  gms Hgb per 100 cc), RBC 4,770,000, WBC 5,400. The differential count was not unusual. There was considerable anisocytosis and achromia of red cells. Platelets were normal. The patient took liberal amounts of liver in her diet several times a week. On January 11, 1927, the hemoglobin was found to be 70 per cent, RBC 4,700,000, WBC 6,050. The smear revealed a differential count as follows: polymorphonuclears 67%, eosinophiles 2%, monocytes 5%, lymphocytes 34%, unclassified 2%. These latter were mononuclear cells with large nuclei, and scattered cytoplasmic gran-

ules which were not azurophilic. Platelets appeared to be reduced in number.

An attempt was made to improve the anemia by diet from January, 1927, to October 15, 1928. She took liver three times a week throughout this period. On February 23, 1928, the patient suffered from an attack of facial erysipelas lasting for five days. On discharge the blood count, February 27, 1928, was as follows: hemoglobin 58 per cent, RBC 4,250,000, WBC 7,200.

On October 19, 1928, the color index was still found to be low, so that it was decided to try the effects of massive doses of Blaud's pills, of which 12 were taken daily for 30 days. This is equal to 10.44 gms of iron.

The successive blood counts were as follows:

Date	Hemoglobin per cent	RBC $\times 10^6$	Color Index
1928			
Oct 19	57	5.25	0.54
Oct 29	65	5.06	0.64
Nov 14	78	5.00	0.78
Nov 17	85	5.52	0.77
1929			
Feb 9	81	4.51	0.89
Apr 4	82	4.86	0.84

The patient remarked that her feeling of perpetual fatigue was relieved for the first time in her memory since early childhood. The spleen was no longer palpable. She has retained excellent health by occasional resort to iron administration.

*Case No. II C F, No. 3950.* A young married woman, aged 35 years, was admitted to the hospital on July 15, 1929, complaining of painful swollen joints, anemia, and

weakness. The arthritis, first noted two years before, had involved first the hands, and later many other joints. The course of the arthritis was one of exacerbations and remissions, during which the joints did not return to normal. Each exacerbation left the joints involved more disabled, more swollen and deformed. A marked exacerbation followed the birth of her fourth and last child, six months before admission. This attack was febrile and she recalled having night sweats. Each of her five pregnancies had been associated with marked ill health. The first terminated by miscarriage. The remaining four gave birth to children, now aged 11, 8, and 6 years and 6 months. The last four pregnancies and labors were normal, except that each left her so "run down" that it required many months for recovery. There was no history of abnormal blood loss, no jaundice, nor purpura. The catamenia had been normal in every way, except that menstruation had not been re-established since the birth of the last child. The past history revealed nothing of significance not included in the foregoing resume. One sister suffered from a similar illness.

Physical examination revealed a small moderately emaciated woman, with brownish skin, but bluish white sclerae, and extremely pale mucous membranes. There was no evidence of purpura, or edema, or general enlargement of lymph nodes. There was an obvious deforming arthritis of the hands, with some muscular atrophy, spindle shaped joints with thin atrophic skin covering periarticular swellings, not acutely tender but somewhat limited in motion and showing malalignment of phalanges.

TABLE I. SUMMARY OF DATA OF CASE I

Date	Hgb %	RBC $10^6$	Color Index	Lower Size	Upper Size	Spread	Apex	Mean*	Median	Standard Deviation
10-10-28	57	5.25	0.54	4.345	8.255	3.910	6.683	6.3032	6.0356	0.7095
4-1-29	82	4.86	0.84	5.214	9.550	4.335	6.152	7.2851	7.0071	0.8217
7-15-29	85	4.68	0.89	5.214	9.124	3.910	7.283	7.2315	7.0770	0.6728
11-7-29	81	4.68	0.89	6.683	8.690	2.007	6.052	7.1933	7.0057	0.5135

\*The difference between means 1 and 2 divided by the square root of the sum of the squares the probable error of means 1 and 2 gives a value of 1.887 which is significant statistically.



Only positive findings of the regional examination are given. Most of the teeth had been extracted, the few remaining in the lower jaw showed marked pyorrhea. The tongue seemed rather smooth on its edges. The tonsils were small, but the faucial pillars were somewhat red and injected. No abnormality of the lungs or heart was found, except a soft apical systolic murmur which was not transmitted beyond the precordium. The spleen was palpable 5 cm. below the costal margin, presenting a typical notch and a hard smooth surface. The liver and kidneys were not palpably enlarged. There was diastasis of the rectus muscles but no ascites. The cervix uteri was deeply scarred. The neurological examination revealed sluggish knee jerks. The ankle jerk could not be elicited. Postural and vibratory sensations were normally perceived.

The blood counts were as follows: hemoglobin 40 per cent (6 gm hemoglobin per 100 cc), R B C 3,950,000, W B C 3,320. The differential count showed polymorphonuclears 63 per cent, lymphocytes 26 per cent, eosinophiles 1 per cent, basophiles 2 per cent, monocytes 6 per cent, and neutrophile metamyelocytes 2 per cent. The red corpuscles showed considerable anisocytosis and achromia with little poikilocytosis. The icterus index of the blood plasma was normal. A fragility test with hypotonic salt solution showed hemolysis beginning at 0.46 per cent, and complete at 0.36 per cent NaCl. The Wassermann and Kahn tests on the blood were negative. The urine contained a trace of albumin but no sugar, urobilin, or blood. A few hyaline casts were seen. The gastric analysis revealed *no free hydrochloric acid* in the fasting contents, or after a test meal of 7 per cent ethyl alcohol. A roentgenogram of the hands revealed atrophic changes in the epiphyses and of the small bones of the wrist. One of the chest revealed no abnormality of the heart. The markings at the root of the lung were somewhat increased in density.

The treatment of this patient was partly directed toward the arthritis and partly toward the anemia. For the former she was given neocinchophen and intravenous injections of amiodoxyl benzoate. The treatment of the anemia consisted, at first, of addition

to the diet of two vials daily of a liver extract known as "secondary anemia" extract, (15), differing from the one commonly known as the Minot-Cohn extract No 343. The diet was a mixed diet known as "House Diet" in the hospital. This diet varies greatly from day to day. It furnishes about 80 gm protein, 2500 calories and 8-15 mgm iron (Estimated). Twenty-four vials of the liver extract were given between July 17th and 29th. The blood counts at the beginning and end of this period were as follows: July 17th Hgb 40 per cent, R B C 3,950,000, W B C 3,320, on July 29th Hgb 45 per cent, R B C 4,000,000, W B C 4,000. During this period in which five blood counts were made, the reticulocytes were always less than 1 per cent. In the amounts given the "secondary anemia" liver extract (15) produced no demonstrable effects. It was discontinued.

On July 30, 1929, the patient was given mass of ferrous carbonate 10 gm four times daily for 30 days, making a total of 120 gm equivalent to 42 gm ferrous carbonate. Marked improvement occurred as is shown by the following blood counts:

Date	Hgb per cent	R B C $\times 10^6$	Reticulocytes
1929 July 29	45	4.00	less than 1%
Aug 2	50	4.00	
Aug 7	60	4.12	
Aug 8			2%
Aug 12	70	4.88	3%
Aug 17	72	5.05	1%
Aug 23	70	4.55	
Aug 30	85	4.85	

The spleen was somewhat reduced in size but still palpable at the costal margin. Subjectively the patient felt better and was discharged from the hospital much improved. Administration of iron was not continued. Six weeks later, Sept 16, 1929, her blood count was Hgb 84 per cent, R B C 3,960,000.

Again she was given mass of ferrous carbonate gm 20 daily. When seen October 25, 1929, the blood count was as follows: Hgb 84 per cent, R B C 4,740,000. At this time her appearance was much improved but she still suffered from her arthritis.

TABLE 2 SUMMARY OF DATA IN CASE II

Date	Hgb %	RBC 10 <sup>6</sup>	Color Index	Lower Size	Upper	Spread	Apex	Mean*	Median	Standard Deviation
7-15-'29	45	3.91	0.56	4.779	9.124	4.345	6.083	6.4507	6.1686	0.7007
7-20-'29	40	3.05	0.65	5.214	9.559	4.345	6.952	6.9172	6.666	0.7396
10-11-'29	84	3.93	1.06	5.214	8.690	3.476	7.821	7.3488	7.1456	0.5823
10-28-'29	84	4.74	0.88	5.648	9.559	3.911	7.821	7.5062	7.2779	0.5973

\*The difference between means 1 and 4, divided by the square root of the sum of the squares of their probable errors is 19.85, which is statistically significant

*Case 3 C O No 3213* A young woman aged 19 years, unmarried, was admitted to the hospital Oct 4, 1926, complaining of a "gnawing feeling in stomach" before meals, gaseous "indigestion" with belching and pyrosis, and occasional attacks of vomiting. This condition had been complained of for at least 8 years. The appetite was good. The bowels were habitually constipated. She had never had jaundice, clay colored, tarry or bloody stools.

For five years she was notably pale, and her pallor had been treated by means of a diet of milk and eggs and small doses of iron, without apparent success. Her weight remained stationary between 115 and 120 lbs. The only other symptoms were a perpetual feeling of fatigue, dyspnea on exertion, and, for 8 months preceding admission edema of ankles had been noted.

The past history and review of symptoms yielded little additional information. The patient had measles as a small child, and whooping cough at age of 6 years. The family history had no bearing on patient's condition.

On physical examination the positive findings were as follows. The patient was a well developed, well nourished white girl of 19. Her skin of faint olive tint, smooth and of fine texture, was pale. The mucous membranes were markedly pale. The sclerae were bluish white. The hair was thin. The nasal half of right eyebrow was missing. The pubic hair was of masculine distribution. The voice was deep and rather harsh. No general glandular enlargement was found. There was slight pretibial edema. The regional examination revealed few other abnormalities. There was considerable pulsation in the vessels of the neck. The heart was normal in size, rate and rhythm. A

systolic blowing bruit limited to the apical portion of the precordium was heard. The blood pressure was 108 mm Hg systolic, 60 diastolic. The abdominal examination was negative except that the tip of the spleen could be felt distinctly on deep inspiration. The pelvic and rectal examination revealed a retroverted uterus. The deep and superficial reflexes were normal. Vibratory sense was well perceived.

The urine was normal on routine examination. The stools contained no blood, ova or parasites. The blood Wassermann reaction was negative. Hgb 55 per cent (7.25 gm per 100 cc.) RBC 4,310,000 WBC 6,880. The differential count was not abnormal. The red corpuscles showed slight anisocytosis. Platelets were present in moderate numbers. The cell volume by hematocrit was 38 per cent. The fragility of the red cells to hypotonic salt solution was not abnormal. The van den Bergh test showed no increase in bilirubin in the plasma.

The gastric juice on two examinations contained no free hydrochloric acid in fasting specimens or after an Ewald meal. Spinal puncture yielded a normal fluid, with no increase in number of cells, or protein. Wassermann test and colloidal gold curves of the fluid were normal.

The roentgenologist reported no abnormalities of the gastro-intestinal tract after investigation by a barium meal. The spleen was seen to extend below the costal margin but did not appear to be very large. A cholecystogram was made subsequently, March 30, 1927, which revealed a normal functioning gall bladder.

A determination of the basal metabolism on March 6, 1927, was reported as -5.8 per cent (Ash and Diller standard).

The treatment of this patient is under

forms of therapy for the anemia is outlined below

and no tubercle bacilli were found on guinea pig inoculation A roentgenogram of the

DATE	Hgb 100% = 15 gm	R B C $\times 10^9$	REMARKS ON PROGRESS AND THERAPY
Oct 5, 1926	55	4 31	Given dilute IICl with meals
Dec 2, 1926	55	4 75	3 Bland's pills daily
Jan 14, 1927			Sodium cacodylate — 2 weeks
Mar 29, 1927	55	4 59	Radiation from carbon arc three times weekly to May, 1927
Apr 5, 1927			Platelets 340,000 Reiman's method
Apr 25, 1927	68		Icterus Index 7
May 24, 1927	70		Started taking liver, $\frac{1}{2}$ lb daily
June 22, 1927	72	5 50	Spleen no longer palpable
Feb 7, 1928	70	4 89	Liver diet discontinued Given 300 Bland's pills Dose XII pills per diem
June 19, 1928	93		Feels well Able to work
Dec 19, 1928	90	4 96	Lost 17 lbs in weight
Feb 8, 1929	83	4 94	

*Case 4 J R Unit No 30389* A married woman aged 30 years, was admitted Dec 7, 1929, and discharged March 3, 1930, to a sanatorium for tuberculosis The immediate cause of admission was pyuria, which examination revealed to be associated with a pyonephrosis of the left kidney The history indicated exacerbations and remissions of a urinary tract infection over a period of eight years, starting with an abortion The infecting organism was *B Coli communis* All attempts to find tubercle bacilli in the urine by smear or guinea pig inoculation failed During the course of observation in the hospital the patient developed pain in the right side of the chest and abdomen, with signs of atelectasis of the right lower lung, followed by a right pleural effusion This was aspirated and blood tinged fluid was removed The cell count of this was as follows R B C 2,500, W B C 4,500 of which 70% were polymorphonuclears, and 30% were mononuclears It was sterile on culture and smear,

chest, made before the onset of the pleurisy, revealed rather heavy shadows at the roots of the lung, and slight evidence of parenchymal tuberculosis under the right clavicle

On admission it was found that the patient had a marked chlorotic anemia The hemoglobin was 40 per cent (5.9 gm per 100 cc), R B C 4,200,000, W B C 7,000 In common with the other patients in this series she had a persistent *achlorhydria*, and a *palpable* spleen Under treatment directed mainly toward the relief of her anemia, the infection of the urinary tract improved, and the pleural effusion disappeared She was transferred for convalescent care to a sanatorium for tuberculosis as a suspect, on account of the pleural effusion, loss of weight of 20 lbs in seven months preceding admission, and the occasional occurrence of night sweats

The response of the patient to the various forms of treatment of her anemia is given below

Date	Hgb $\times 10^6$	R B C	REMARKS ON PROGRESS AND THERAPY
Dec 7, 1929	40	4 24	W B C 7,400 Differential PMN 56, Lymph 30 Eosin 1%, Basoph 1%, M & T 8%, myelocytes 4% Reticulocytes 2.3% Marked poikilocytosis and anisocytosis Iron and ammonium citrate 60 gm daily to Dec 24, 1929 Reticulocytes varied 2-4 per cent
Dec 24, 1929	40		Transfusion 500 cc citrated blood
Dec 30, 1929			Bland's pills XII daily to Jan 8th
Jan 8, 1930	67	5 25	Vallet's mass of ferrous carbonate 250 gm, given from Jan 8th to Feb 12, 1930
Jan 18, 1930	73	5 88	
Jan 22, 1930	78	5 43	
Jan 25, 1930	81	5 66	
Jan 29, 1930	87	5 57	
Feb 21, 1930	97	5 87	

*Case 5 G D No 35672* A married woman 58 years old, was admitted to the hospital May 27, 1930 Complaining of "diarrhea" and "anemia" The onset of her illness was four months before admission, with the passage, three or four times a day, of semiformal stools containing large amounts of mucus She became very weak and felt her heart pounding Her physician found that she was anemic For two months prior to admission she was treated intensively with liver, liver extract No 343, and "ventriculin," without appreciable benefit The bowel movements decreased slightly in frequency and occurred without pain or tenesmus She complained bitterly about vague but horrible abdominal sensations, of borborygmi, and of difficulty in passing flatus She recalled a similar episode of weakness, anemia, and diarrhea at the age of 30 following childbirth, from which she did not recover for 9 months After each of her four pregnancies she became anemic and had a recurrence of loose stools There are many irrelevant details in the history which are omitted here The patient was in the habit of chewing tea leaves almost incessantly

Examination revealed a well developed and well nourished woman of 58, who appeared chronically ill Her skin was dry, rough, inelastic, and of a bronzed color The mucous membranes and nail beds were very pale The sclerae were not jaundiced There was no general glandular enlargement, nor edema The nails showed a well marked koilonychia The heart was somewhat enlarged and a soft systolic bruit was audible from the apex to the pulmonary area The lungs were normal In the abdomen a markedly enlarged spleen could be felt descending on inspiration from 5 to 8 cm below left costal margin There was a rounded mass in the right flank, which was probably the right kidney The liver edge descended slightly below the costal margin The tendon reflexes were all normal, as were the plantar and abdominal reflexes Vibration was well perceived

The blood count was as follows Hgb 37 per cent (5.5 gm per 100 cc), RBC 3,660,000 WBC 3,000, with a normal differential count Reticulocytes 3.7% The red corpuscles were pale and showed some variation

in size and shape Platelets were normal The saliva contained 770 leucocytes per cu mm so that it was evident that the leucopenia was not of the aplastic type (2) The urine and stools were not abnormal in any way

The blood sugar, from a fasting level of 90 mg per cent, rose to 185 mg in 45 minutes, and was 172 mg at the end of 2 hours and 15 minutes after the ingestion of 100 grams in glucose The icterus index was normal, 12, 4 A test of liver function was done by injection of "bromsulphalein" At the end of 5 minutes 15 per cent, and at the end of 30 minutes 10 per cent of the dye remained

A roentgenological examination of the gastrointestinal tract with a barium meal revealed no local lesion The stomach showed the indentation of an enlarged spleen The diagnoses considered were

- (1) Hemochromatosis The evidence for both cirrhosis and diabetes was insufficient to support this
- (2) Banti's syndrome Again the evidence for cirrhosis was insufficient
- (3) Achylic chloranemia The prompt response of the anemia to iron in large doses tends to support this diagnosis, as does the history of earlier episodes of anemia

The patient was given 12 Blaud's pills, containing 350 milligrams of iron, daily Of the numerous blood counts made to mark the progress of response to therapy only six will be recorded here On each of these six occasions measurements were made of the red cell diameters in fixed blood smears and these data plotted as Price-Jones curves as shown in Figure I

A summary of the statistical value of the data, correlating the mean cell diameters with the blood counts and color indices on six occasions, is given in table 1 This summary shows clearly that as hemoglobin and color index rose, in response to treatment with Blaud's pills in large doses, a corresponding increase in mean diameter of red cells occurred which is statistically significant that which is statistically significant

## DISCUSSION

The five cases described here all have many features in common. The presenting complaints were varied, two were chiefly gastro-intestinal, one of anemia, and two of chronic infections. The third case was one of undoubted chlorosis. The remaining four cases in older women gave indications in the

history of probable anemia in childhood or adolescence, though definite data on this point were not available, these patients may represent the recurrence of chlorosis in later life. In all of the histories specific inquiry as to known blood loss, purpura, chronic or recurring jaundice revealed none of these. Four of the five patients had

TABLE 3. SUMMARY OF DATA IN CASE V

Date 1930	Hgb %	RBC $\times 10^6$	Color Index	Lower Size	Upper Size	Spread	Apex	Mean*	Median	Standard Deviation
June 1	36	3.80	0.47	4.345	8.690	4.345	6.952	6.684	6.4860	0.6815
3	37	3.66	0.50	3.910	9.559	5.649	7.386	7.0311	6.8301	0.7973
6	52	3.83	0.67	5.214	9.993	4.779	7.821	7.2315	7.0551	0.8290
21	70	4.93	0.71	5.214	8.690	3.476	7.821	7.3502	7.1535	0.6465
28	85	5.49	0.77	5.214	9.124	3.910	7.821	7.5661	7.4170	0.7214
July 5	87	5.31	0.82	5.648	9.993	4.345	7.821	7.7524	7.5675	0.6800

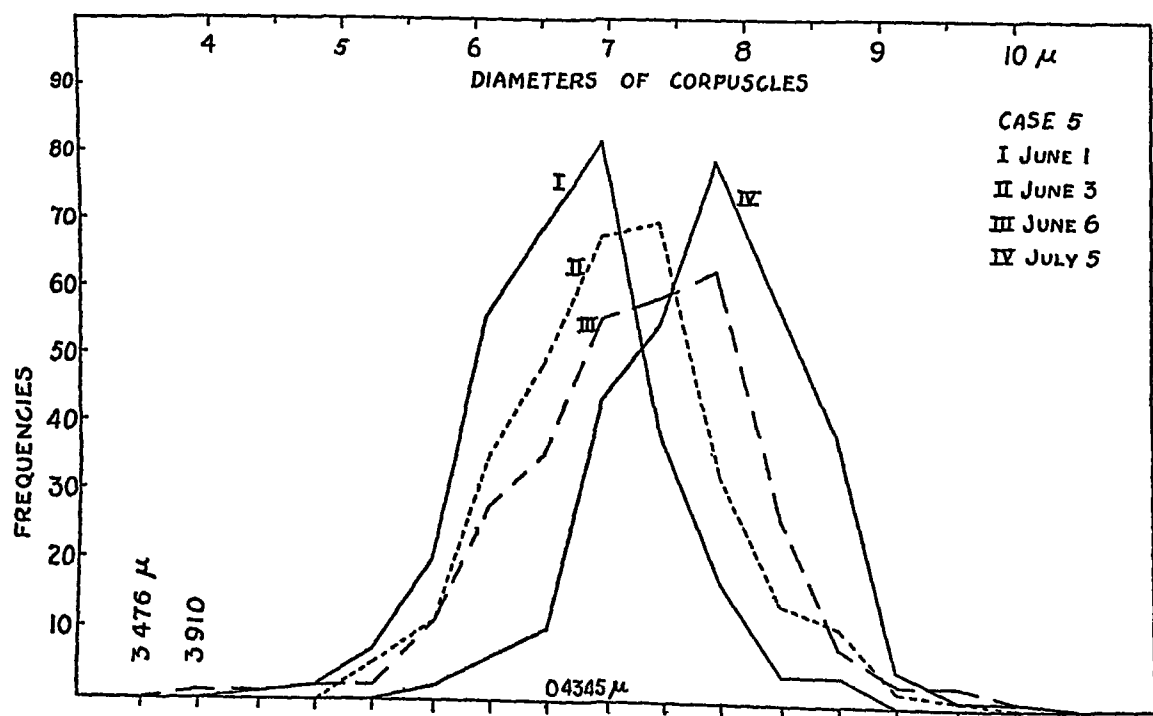


FIG 1 Price-Jones curves of the frequency of distribution of corpuscular diameters in Case 5, made successively to show the increase in mean diameters as the patient responded to large doses of iron

borne children and each of these described periods of anemia *following* child bearing

Examination of all five patients revealed a palpable enlargement of the spleen. In three only the tip was felt. In two the enlargement was sufficient so that the notch could be identified. The color of the skin was abnormal enough for comment in three of the five, the description varied from sallowness, olive tinted, to bronzed. In none of the patients was there evidence of jaundice, nor of purpura. In none were the lymph nodes generally enlarged. In one case, only, the tongue was unusually smooth on its lateral borders. In no case were the neurological findings indicative of spinal cord lesions. All five patients perceived vibration perfectly.

One patient had a chronic deforming arthritis, with epiphyseal decalcification and periarticular changes. Faber and Gram (1) record eleven cases of such a combination of chlor-anemia with achylia gastrica and arthritis deformans, and comment on the frequent association of achylia and this form of arthritis.

In all cases examination of the stools failed to reveal occult blood. The gastric analyses in all cases showed no free hydrochloric acid while fasting or after a test meal. No attempt was made, however, to bring forth acid secretion by the administration of histamine. Hence, the term achlorhydria has been used rather than achylia gastrica in connection with our cases. In two patients with gastro-intestinal symptoms roentgenological examination of the gastro-intestinal tract and gall bladder failed to reveal anatomical

abnormalities. The blood picture was essentially the same in each case, the outstanding feature being the low color index, about 0.5. In no case was the red cell count below 3.8 millions. The lowest hemoglobin was 36 per cent or 5.4 gm per 100 cc. Two of the five patients showed a leucopenia. In the other cases the leucocyte counts were normal. In case 5, in which leucopenia was noted, salivary counts were done, as recommended by Isaacs (2), which showed a clear excess of salivary leucocytes indicating that the leucopenia was not of the aplastic type.

The differential counts revealed a slight relative lymphocytosis. Platelets appeared to be normal in the smears, and there was no evidence of platelet deficiency in bleeding or clotting mechanisms. There was very little poikilocytosis. Anisocytosis was definite but in no case extreme. Polychromatophilia was observed before treatment only in case 5, the patient having taken larger amounts of liver extract. No. 343 before coming under observation. On the initial examination 37 per cent of the erythrocytes were reticulated in this case.

The serum was tested in each case for bilirubin by determination of icterus index, or the van den Bergh test, or both. In no case was an excess found.

The data for Price-Jones curves of the frequency of distribution of corpuscular diameters are given in tables I, II, and III. The mean diameters of corpuscles in these three cases before treatment were 6.30, 6.15 and 6.68 microns, respectively. As a result of counts of 10,000 cells in 20 normal individuals Price-Jones gives the nor-

mal mean diameter as  $7.21\mu$ . After the color index had risen in response to iron administration the mean diameters of the same three cases were 7.36, 7.51, and 7.75 respectively. The Price-Jones curves of cases 5 have been presented graphically in Fig. 1, showing clearly the effect of increasing hemoglobin content upon cell diameters.

### Treatment

Four of the five patients were first treated with liver extracts or by addition of liver to the diet.

The first patient took  $\frac{1}{2}$  lb of liver three times a week for nearly two years. At first there was a moderate increase in hemoglobin but at the end of the period the blood count was practically at the starting level, with a very low color index. The third patient likewise took liver over a considerable period with some improvement in both red count and color index, which was slight compared with the changes that occurred after administration of Bland's pills in large doses. The second patient was given a "secondary anemia extract" of liver, which was found to be potent in causing regeneration of blood in the chronic post-hemorrhagic anemia of dogs in the experiments of Whipple, Robschert-Robins and Walden (15). This extract produced no signs of regeneration in case 2. The fifth patient was intensively treated with liver extract 343 (Lilly) and also with "ventriculin," an extract of stomach introduced by Sturgis and Isaacs (11), without curative effect. The presence of an increase in reticulocytes was the only observed effect of this treatment.

The response to iron, given in large

doses in the form of Bland's pills or Vallet's mass of ferrous carbonate, was clear cut and prompt in all cases. By analysis the Bland's pills used contained in each 29 mg of iron, so that in giving 12 pills daily approximately 350 milligrams of iron were given. This amount of iron is ten times the amount found by Sherman (10) in that American dietary richest in iron, and fifty times the poorest, and at least twenty times the amount generally sufficient for the maintenance of normal men.

The mechanism by which the administration of this excess of iron produces its curative effects in chlor-anemias, has long been a subject of speculation and study. A review of the many opinions and observations is impossible. The most recent developments in connection with iron metabolism notably the discovery by a group of workers in Wisconsin, in association with Steenbock and Hart (13), that copper in small amounts is an essential to the utilization of iron in the nutritional anemia of rats. These authors were unable to secure curative effects when purified iron salts were administered. If copper were present in small amounts as an impurity, or were added to the purified iron salts, prompt curative effects of iron were obtained. In this connection it is important to note that the Bland's pills used by us were found by analysis to contain 0.03 mg of copper per pill, so that *our patients received 0.36 mg Copper diem when Bland's pills were given*.

We have been unable to find other studies of the effect of iron in which the presence of copper has been ex-

cluded The experiments of Whipple and Robscheit-Robbins (16), would indicate practically no curative effects of copper added to the basic diet plus a salt mixture without iron, given to dogs rendered chronically anemic by hemorrhage On the other hand, the presence of copper as an impurity in the iron salts administered is probable

One remaining feature is of interest Many years ago, Romberg (9) called attention to the fact that there is a high content of water in the tissues of chlorotics Two of our patients, who were not edematous, lost 17 and 30 lbs of weight respectively, after the completion of the iron therapy

#### CONCLUSIONS

1 Five cases of chlorotic anemia, with achlorhydria, palpable spleens, an-

emia with low color index and corpuscles of small mean diameters, are described

2 Treatment with liver and liver extracts produced little or unsatisfactory curative effects

3 Treatment with large doses of inorganic iron in the form of Bland's pills or Vallet's mass was strikingly and promptly effective

4 Price-Jones curves of the frequency of distribution of diameters of red corpuscles reveal abnormally small mean diameters, and that these increase to normal as the color index rises in response to treatment

5 The preparations of iron used contained copper as an impurity

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# The Blood Platelets in Pernicious Anemia After Liver Therapy\*

By SAVAS NITTIS, *Ann Arbor*

ALL morphological constituents of the blood in pernicious anemia show quantitative changes with the onset of a remission

The present study deals with the changes in the numbers of the blood platelets in the relapse and during the development of remissions induced by liver therapy

## METHODS OF STUDY

In the beginning of this study different so-called "wet methods" for counting blood platelets were employed. They were soon found to be difficult to execute and inconsistent in their results. A "dry method" was then employed that not only gave fairly satisfactory results but also had the advantage of permitting the counts to be carried out at any convenient time, and the specimens could be kept on file for future reference. As there was no attempt made to record the exact number of the blood platelets present, but only to notice the relative changes in their number, the counts were carried out on the smears prepared for the routine study of the blood of the patients in this Institute.

The films were prepared as follows. Brilliant cresyl blue in 0.3% alcoholic solution was spread on clean cover-slips that had been kept in ether, and allowed to dry. The dye side of the cover-slip was then polished on type-writer paper. A drop of blood was then placed near the edge of a clean cover-slip which was inverted and placed over the cover-slip which had been prepared with the dye. After the blood had spread evenly between the slips to their edges, and the stain was well mixed with the blood, they were pulled apart and allowed to dry. They were then counterstained with the Wright's stain and mounted with Canada balsam or gum dammar.

The number of platelets accompanying one thousand red blood cells was noted. This number multiplied by the number of thousands of the red blood cells present in a cubic millimeter was taken as the total number of the blood platelets in a cubic millimeter. Since the platelets are not always distributed evenly upon a film, the microscopic field was limited so that many spots could be used. Counting was done on more than one film. The four corners, the middle and intermediate spots were always used. To avoid error as selections of spots the eye was taken off the microscope while shifting the film.

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\*From the Thomas Henry Simpson Memorial Institute for Medical Research of the University of Michigan, Ann Arbor, Michigan.

for new fields. No field was abandoned unless it was impossible to count either of the elements. Effort was made to make an accurate count even when a congested area was met. Counts with this method and with two wet methods (Hayem, and Rees and Ecker) compared fairly well in both healthy and sick individuals, as the following count from a case of hemolytic icterus shows

Red blood cells	2,800,000
Blood Platelets	142,000 (Hayem)
	134,000 (Rees and Ecker)
	147,000 (Dry smear count)

The exact number of the blood platelets in the healthy individual is not as yet agreed upon. The majority of the authors give it as between 200,000 and 300,000 per cubic millimeter, although figures as low as 150,000 and as high as 500,000 per cubic millimeter are quoted in the literature as normal. The method here employed gave fairly constant figures for the same individual in many successive counts, but varied considerably from person to person. The figures below, representing counts from two healthy male persons of the same age, members of the staff of this Institute, made on corresponding days by the same technic and technician, emphasize these variations in different individuals.

All counts in the healthy individuals showed the variation in the blood platelet count to be greater than the red or even the white blood cell count. But however inaccurate these figures

may be, they are of comparative value, although possibly to a less degree than the white or red blood cell count. All smears were made by the same individuals, employing the same technic, and all platelet counts were made by the same person. This eliminated, to a certain degree, personal errors.

DATA

It was observed that the number of the blood platelets in pernicious anemia before starting treatment was always less than the lowest given normal count. Their number appeared to be inversely proportional to the degree of anemia present but this did not seem to follow a definite rule. When the red blood cell count was below one million the platelets were found to be below 100,000 and at times even less than 10,000 (Table I). It was observed however that with this same technic the number of the blood platelets were found in some cases to be less than 100,000 even after remission and for many days following it (Chart I). But irrespectively of the initial number of the blood platelets there followed a rise after effective liver therapy. This rise occurred either before (Table II, Chart I), with (Table III, IV and V), or after (Chart II, Table I and VI) the reticulocyte rise, but always before the rise of the blood cells. In cases where the platelet rise preceded that of the reticulocytes there was usually another rise, at times higher than the first, oc-

S N

Red blood cells	5,560,000	5,810,000	5,840,000	6,430,000	6,050,000
Blood platelets	302,000	255,000	280,000	289,000	314,000
M R					
Red blood cells	5,630,000	5,670,000	5,350,000	5,560,000	5,590,000
Blood platelets	170,000	119,000	113,000	189,000	122,000

curing several days after the reticulocyte rise (Table V). The rise in the number of the blood platelets was a constant phenomenon but in no two cases appeared exactly alike. It did not follow as definite a law as the red blood cell count and the hemoglobin or as the reticulocyte percentage. The fluctuations in their number were as irregular as those of the white blood cells. No gross correlation was observed to exist between the red blood cell, the reticulocyte forms or the white

blood cells. Like the red and white blood cells, the platelets were decreased during relapse. In some cases a high platelet count, as compared to the count found in the initial stage of the disease, was found at a second relapse (Table III). Again like the red and the white blood cells they showed a rise during either a spontaneous remission or one induced with liver therapy. But unlike both these elements, they increased beyond the normal level, at times reaching three or four times

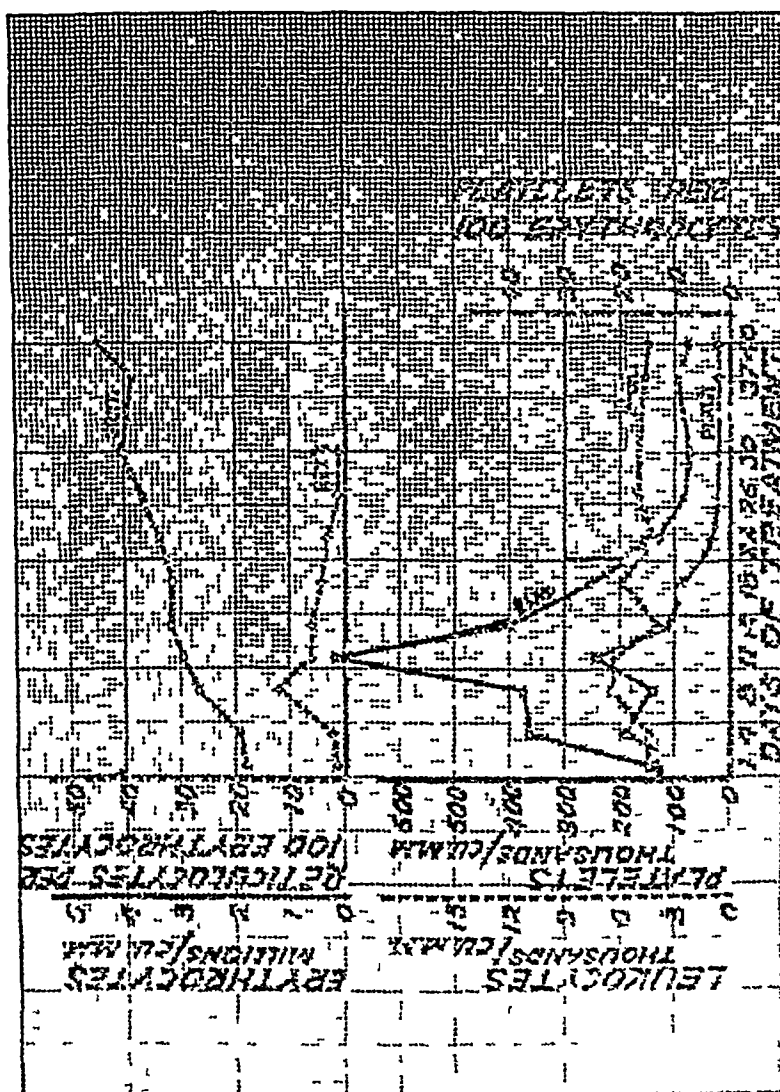


CHART I

the normal count (Table III and V), and then decreased. The drop was as irregular as the increase and in some cases it did not stop at the normal level but went below it. (Chart I, Table IV). In a few cases, for many days following remission the blood platelet number continued to be below the normal level (Table IV, Chart I). In other cases it was slightly above this (Table II) and in some cases it corresponded to the counts found in normal individuals. The variations in

the number of the blood platelets present before commencement of treatment appeared to be independent of the clinical picture of the disease and likewise patients with parallel responses in the blood platelets during the progress of liver therapy showed no marked apparent similarity in the improvement of the clinical symptoms.

Of interest is the case presented in Table I. To this patient 30 bottles of Lilly's liver extract, made from 3000 grams of liver were given by means of



CHART II

TABLE I

Days of Treatment	Erythro Millions per cu mm	Hemoglobin % (Sahli)	Reticulo- cyte %	Leukocytes per cu mm	Platelets per cu mm	Platelets per 100 Erythrocytes
	710	13	16	4,500	22,000	3.2
1	690	15	21	4,900	18,000	2.6
2	402	12	9	4,100		
3	690	12	25	9,900	8,000	1.2
4	720	12	16.0	22,000	6,000	.8
5	1,190	18	42.0	8,800	5,000	.4
6	1,400	20	45.0	4,750	8,000	.6
7	1,590	29	27.0	3,800	22,000	1.4
8	1,710	33	20.0	6,400	65,000	3.8
9	1,360	28	11.7	6,550	106,000	7.8
10	1,590	29	4.7	5,950	159,000	10.0
11	1,780	34	1.3	3,700	256,000	14.8
12	1,530	30	.6	2,650	186,000	12.2
13	1,990	30	.4	1,550	314,000	15.8
14			.1			
17	1,480	30	1.1	2,850	62,000	4.2
20	1,980	30	4.2	3,000	67,000	3.4
24	1,750	40	4.8	5,800	112,000	6.4
27	1,330	43	2.5	11,500	88,000	6.4
31	1,820	40	.1	4,400	386,000	21.2
33	2,400	42	.1	6,250	500,000	20.4
76	3,600	78	.1	5,150	317,000	8.8
6 Mo	4,900	90		9,550	632,000	12.9
12 Mo	5,450	93		7,900	518,000	9.5

a stomach tube on the first day of treatment. No more liver was given for twelve days. The platelet count which was very low rose from an average of 10,000 per cubic millimeter to 314,000 per cubic millimeter thirteen days following the administration of the liver extract. The highest reticulocyte percentage was found on the seventh day following the administration of the liver. On the thirteenth day 30 capsules of liver extract representing 480 grams of fresh liver, were given. This dose was repeated daily thereafter. From the thirteenth to the thirtieth day the platelets were below 100,000 per cubic millimeter, then they increased again reaching

500,000 on the 33d day. This second and higher rise might be related to the second reticulocyte rise which on the 24th day was 5%. After twelve months the platelets were still above 500,000 per cubic millimeter. In this, as in all tables and charts published here the counts were made daily. The intermediate counts were omitted from the tables in the interest of clarity and economy of space.

In most cases the blood platelets during the initial period of the disease or during relapse were usually of a very small size. At times, however, platelets of larger size were observed. In some cases also, at times, following remission of the disease, the

TABLE II

Days of Treatment	Erythro Millions per cu mm	Hemoglobin % (Sahli)	Reticulo- cyte %	Leukocytes per cu mm	Platelets per cu mm	Platelets per 100 Erythrocytes
1	1 220	22	8	4,800	167,000	13.8
3	1 370	23	15	3,250	559,000	40.8
5	1 260	26	81	4,150	247,000	20.4
6	1 240	26	17.8	2,850	79,000	6.4
7	1 166	26	25.6	2,360	156,000	9.4
8	1 990	35	16.6	2,250	242,000	12.6
9	2 650	39	10.5	3,150	234,000	12.6
10	2 660	42	4.4	3,950	293,000	11.0
11	2 370	44	5.7	4,500	223,000	9.4
12	2 170	48	6.0	5,050	295,000	13.6
13			2.4			
14	2 570	52	6.2	4,100	264,000	10.2
15	2 760	52	9.1	3,550	502,000	18.2
17	3 460	51	2.3	6,150	623,000	18.0
20	3 100	49	2	3,750	322,000	10.4
26	4 030	66	1	6,950	572,000	14.2
29	3 930	60	1	4,350		
60	5 270	60		10,300	857,000	16.2
200	4 950	76		9,550	416,000	8.4
300	4 890	78		7,550	398,000	8.2

therapy, it was observed that the size of the platelets followed a definite cycle although of an irregular rhythm. The giant forms, which at times were of the size of normal erythrocytes, were followed by the appearance of medium sized platelets, which in turn were followed by the appearance of small platelets, at times of a very minute size. This period was then followed by a shower of larger and giant forms. This was not a constant phenomenon and the cycle was not very regular.

#### SUMMARY

In pernicious anemia the blood platelets are decreased in number but not as uniformly as the red blood cells.

Following remission induced by liver therapy the platelets increase in number, reaching a level higher than normal, after which they decrease. The highest count usually occurs several days after the maximum reticulocyte percentage is reached.

There is no gross correlation between the increase in numbers of the platelets and that of the erythrocytes, the reticulocyte percentage or the number of leukocytes.

Giant forms of blood platelets appear and disappear at intervals in all cases but this phenomenon does not form a markedly regular rhythm.

TABLE III.

Days of Treatment	Erythro Millions per cu mm	Hemoglobin % (Sahlb)	Reticulo- cyte %	Leukocytes per cu mm	Platelets per cu mm	Platelets per 100 Erythrocytes
1	200	27	1	3,500	97,000	81
2	730	27	1	3,550	71,000	98
3	970	26	23	5,030	40,000	47
4	875	27	29	2,700		47
5	1 000	32	43	4,000	50,000	50
6	960	32	69	3,200	121,000	126
7	1 080	32	116	3,900	229,000	212
8	1 250	42	87		273 000	235
9	1 095	50	89	4,050		
10	1 080	45	133	4,450	330,000	306
11	1 195	42	16	4,000	459,000	384
12	1 200	44	97	5,650	343,000	286
13	1 585	41	158	5,050	500,000	316
14	1 420	44	96	5,050	408,000	294
15	1 310	46	53	6,050	498,000	380
16	1 520	41	37	6,550	638,000	420
17	1 755	47	76	5,150	629,000	360
18	1 360	52	32	5,800	571,000	420
20	1 810	53	14	5,000	860,000	474
22	2 100	63	16	6,450	676,000	322
24	2 550	62		5,400	770,000	302
48	3 500	76		4,250	1,225,000	350
78	5 040	84		10,850	554,000	110
124	5 980	83		11,550	478,000	80
9 Mo	2 500	50		12,050	250,000	100
18 Mo	2 800	71		7,250	487 000	174

TABLE IV

Days of Treatment	Erythro Millions per cu mm	Hemoglobin % (Sahlb)	Reticulo- cyte %	Leukocytes per cu mm	Platelets per cu mm	Platelets per 100 Erythrocytes
1	1 09	19	12	2 350	21,000	20
3	77	18	13	3 100	42 000	64
9	1 63	32	320	2 080	563 000	349
17	3 06	41	19	5 550	222 000	74
32	3 80	65	17	6 400	38 000	19
43	3 38	70		9 350	155 000	49
47	4 00	71		8 000	18 000	34
66	5 30	70		10 250	5 000	11
7 Mo	5 15	88		17 250	227 000	24
20 Mo	1 04	60		9 000	865 000	202
27 Mo	1 24	95		5 000	11 000	22



TABLE V

Days of Treatment	Erythro Millions per cu mm	Hemoglobin % (Sahli)	Reticulo-cyte %	Leukocytes per cu mm	Platelets per cu mm	Platelets per 100 Erythrocytes
1	1 49	38	1 9	4,300	89,000	6 0
2	1 69	41	2 6	2,800	60,000	3 6
3	1 59	37	1 7	2,290	73,000	4 6
4	1 49	36	3 0	3,550	220,000	14 8
5	1 89	40	4 6	4,050	108,000	5 8
6	1 76	42	8 1	3,900	211,000	12 0
7	2 02	43	9 7	5,900	157,000	7 8
8	1 90	47	15 2	6,840	213,000	11 2
9	1 66	52	4 9	5,050	803,000	48 4
10	1 94	52	9 3	6,300	608,000	31 4
11	1 89	52	6 4	6,700	665,000	35 2
12	1 86	52	9 1	6,650	681,000	36 6
13	2 67	62	6 0	6,200	844,000	31 6

TABLE VI

Days of Treatment	Erythro Millions per cu mm	Hemoglobin % (Sahli)	Reticulo-cyte %	Leukocytes per cu mm	Platelets per cu mm	Platelets per 100 Erythrocytes
1	0 83	19	2 4	3,350	50,000	6 0
8	1 38	27	25 3	4,500	113,000	8 2
16	2 65	42	2 9	5,750	530,000	20 0
21	2 22	49	1	8,350	543,000	20 4
24	2 98	49		4,800	745,000	25 0
27	3 49	60		7,600	419,000	12 0
30	2 92	60		6,200	350,000	12 0
33	2 88	60		6,350	127,000	4 4
36	4 11	58		8,100	370,000	9 0
39	4 19	59		5,500	168,000	4 0
42	3 87	71		8,350	193,000	5 0
45	3 58	64		9,450	358,000	10 0
48	4 10	69		9,550	615,000	15 0
72	4 88	75		12,200	390,000	8 0
118	5 34	76		7,250	246,000	4 6

# Clinical Consideration of an Anemia of Pregnancy and the Puerperium\*

By C T SMITH, M D, F A C P and W B KINLAW, M D, F A C P,  
*Medical Service Park View Hospital Rocky Mount N C*

**P**UERPERAL anemia, which is probably a continuation if not a progression of the anemia of pregnancy, was first described by Channing in 1842,<sup>1</sup> and for many decades doubted as being a specific anemia, has received more study in the past two decades and has been established as a definite anemia related to pregnancy and the puerperium, and furthermore according to Murdock's<sup>2</sup> observations, "if the patient survives the acute attack, the blood picture usually returns to normal"

For an anemia to merit such a classification, we contend that all anemias should be excluded which might be explained by hemorrhage, sepsis (including infections), nephritis, syphilis, previously present hemolytic icterus, or primary pernicious anemia, leukemia, acute or chronic, myelocytic, or lymphocytic, in other words, all possible causes except the pregnancy itself. We also wish to exclude the so-called toxemia of pregnancy as it is generally known, unless the anemia we are discussing is a manifestation of a toxin produced by the pregnancy.

A most comprehensive clinical picture of this anemia is given by Rowland.<sup>3</sup> "An insidious onset of anemia in the latter weeks of pregnancy, often

not recognized till in the puerperium, usually antepartum symptoms of weakness, breathlessness on exertion, palpitation, headaches, dizziness, edema of the feet, and occasionally an associated definite toxemia of pregnancy with albuminuria and hypertension. Labor may come on prematurely, is characteristically short, and relatively painless. Still-birth may occur, but a living child does not share in the anemia and develops normally. Labor aggravates the anemia, and the patient may go into collapse at once if the anemia is marked. Typically there is a rapid progression in the anemia for the first week or two. Or, it may be slow, requiring two months before recognition. Hematologically primary and hematologically secondary."

Esch<sup>4</sup> insists "the secondary type never goes into the primary type and that however closely the picture may resemble pernicious anemia no authentic case of recurrence independent of pregnancy has yet been reported. Such views are in accord with our findings as a later analysis will show."

In considering the differential diagnosis, the relationship of this anemia to pernicious anemia is often very close. Achlorhydria may be present with diarrhea, sore tongue, glossitis,

in the extremities, and a blood picture closely resembling primary anemia. The very fact that liver extract is helpful in selected cases argues a closer kinship than could have been claimed before. Pepper<sup>5</sup> admits, "unquestionably the evidence favors the view that the anemia is a hemolytic anemia, but no evidence to permit us to designate the hemolytic factor at work." If we accept the theory that pernicious anemia is a deficiency disease, which deficiency is supplied by liver extract, might not certain of the anemias of pregnancy and the puerperium be due to the same but temporary deficiency? We say temporary, because it is generally admitted that when the patient is tided over the acute attack, she will probably remain well—succeeding pregnancies may or may not provoke another attack.

If the anemia of pregnancy is not a toxemia of pregnancy, the resemblance is so close that some of our patients have been sent in as a toxemia for induction of premature labor or Caesarian section. The symptoms of toxemia are the albuminuria, anemia, increased pulse rate, edema, and sometimes hypertension. All of these findings may be present in the anemia of pregnancy. The actual diagnosis may not be made until after the pregnancy has been terminated and the patient fails to make the expected recovery. If the anemia of pregnancy is kept in mind and the condition of the patient justifies the delay, the treatment of the anemia may be instituted and the patient probably carried to term.

The presence of fever, frequently alarmingly pronounced, gives the obstetrician much concern, fearing puer-

peral sepsis. If the case is seen and a diagnosis made before labor, the rise of fever can be prognosticated, and this gives the obstetrician and patient much comfort when there is a persistent elevation of fever after delivery. The ultimate exclusion of sepsis will not be made by the negative blood cultures, which frequently leave one in doubt, but by the rapid fall in temperature and leucocytosis, if present, as the anemia improves under treatment. The absence of leucocytosis does not necessarily eliminate sepsis as a diagnosis, because Cabot<sup>6</sup> and Osler have shown by four autopsy cases that a severe sepsis may be present without including any leucocytosis.

The excessive amount of albumin in the urine would lead the unwary to make a diagnosis of uncomplicated nephritis. We feel that we have made that mistake more than once, with attention and treatment focussed entirely on the nephritis, when, if the anemia had been treated, the albuminuria would have cleared up.

We have nothing distinctive to offer regarding this albuminuria, but suggest that a study of the anemia will most likely indicate the condition requiring the treatment, and the therapeutic response will verify the diagnosis.

If the case is first seen after the anemia has been present for some time, or was slow in appearing, the fever and pronounced cardiac murmur, usually systolic in time, suggest endocarditis. Here again, the response to the treatment of the anemia will establish the diagnosis.

The treatment will depend on the individual case, and if the proper treatment is selected and adhered to, the response is most gratifying. The

anemia might be severe and the patient so ill, that the immediate transfusion is indicated. This might suffice, but it is well to follow up with either liver extract and hydrochloric acid, if achlorhydria is present, or massive doses of iron. We have tried to demonstrate with cases all too few, that the patient without hydrochloric acid in stomach contents, or with a low acidity, will respond better to liver extract, and the patient with normal or high acidity, will not respond to liver extract, but to massive doses of iron. In our earlier cases we transfused, then gave dilute hydrochloric acid, iron, aiseimic, and later when the value of liver extract in pernicious anemia was demonstrated, we used it in the treatment of puerperal anemia.

In the analysis of our twenty-two cases, eight of which were reported in 1925<sup>7</sup>, we find it almost impossible to classify them as primary and secondary types. Seven showed involvement of the gastro-intestinal, the hematopoietic,

and nervous systems (accepting the history of paresthesia as an involvement), two of the gastro-intestinal and hematopoietic. These nine we classified as of the primary type. The remaining thirteen showed such bizarre pictures as to defy classification, save that they were undoubtedly related to the pregnancy and puerperium. Of the nine cases in which gastric analyses were done, five showed no free hydrochloric acid, and in four the hydrochloric acid was below normal.

The blood Wassermann (Kolmer) was negative in eighteen cases, in four it was not done. These patients showed no clinical evidence of syphilis, so with the negative Wassermann reactions, we feel that we have contradictory evidence to syphilis playing any part in these cases.

In this particular section of North Carolina, hook-worm has been very prevalent. This required the exclusion of uncinariasis as a contributing factor in the anemia. In eleven cases

Case No.	Patient	Age	Gravida	Parity	Onset of anemia	Duration of illness	Course	WBC	Hb	RBC	Diff. Count	Spinal Fluid	Pathologic
1	P. B. 1911	22	1	1	1911	1911	1911	1911	1911	1911	1911	1911	1911
2	P. B. 1912	23	1	1	1912	1912	1912	1912	1912	1912	1912	1912	1912
3	P. B. 1913	24	1	1	1913	1913	1913	1913	1913	1913	1913	1913	1913
4	P. B. 1914	25	1	1	1914	1914	1914	1914	1914	1914	1914	1914	1914
5	P. B. 1915	26	1	1	1915	1915	1915	1915	1915	1915	1915	1915	1915
6	P. B. 1916	27	1	1	1916	1916	1916	1916	1916	1916	1916	1916	1916
7	P. B. 1917	28	1	1	1917	1917	1917	1917	1917	1917	1917	1917	1917
8	P. B. 1918	29	1	1	1918	1918	1918	1918	1918	1918	1918	1918	1918
9	P. B. 1919	30	1	1	1919	1919	1919	1919	1919	1919	1919	1919	1919
10	P. B. 1920	31	1	1	1920	1920	1920	1920	1920	1920	1920	1920	1920
11	P. B. 1921	32	1	1	1921	1921	1921	1921	1921	1921	1921	1921	1921
12	P. B. 1922	33	1	1	1922	1922	1922	1922	1922	1922	1922	1922	1922
13	P. B. 1923	34	1	1	1923	1923	1923	1923	1923	1923	1923	1923	1923
14	P. B. 1924	35	1	1	1924	1924	1924	1924	1924	1924	1924	1924	1924
15	P. B. 1925	36	1	1	1925	1925	1925	1925	1925	1925	1925	1925	1925
16	P. B. 1926	37	1	1	1926	1926	1926	1926	1926	1926	1926	1926	1926
17	P. B. 1927	38	1	1	1927	1927	1927	1927	1927	1927	1927	1927	1927
18	P. B. 1928	39	1	1	1928	1928	1928	1928	1928	1928	1928	1928	1928
19	P. B. 1929	40	1	1	1929	1929	1929	1929	1929	1929	1929	1929	1929
20	P. B. 1930	41	1	1	1930	1930	1930	1930	1930	1930	1930	1930	1930
21	P. B. 1931	42	1	1	1931	1931	1931	1931	1931	1931	1931	1931	1931
22	P. B. 1932	43	1	1	1932	1932	1932	1932	1932	1932	1932	1932	1932

in which the stools were studied for ova, they were found in only one, and when that patient returned with a recurrence, the ova were not present.

Fever was present in all the series of twenty-two cases. In nineteen the temperature was 100 degrees F. or over. In one 104 and another 105 degrees. The urine of eighteen showed albumin estimated as varying from 1 to 111 on a scale of 14.

In twenty-one cases the red cell counts were below three million, in sixteen of these below two million, and in four of these below one million. The color index was greater than one in thirteen cases. In sixteen the smears showed definite anisocytosis and poikilocytosis. Nucleated reds were found only once and then there were 263 to each 100 white cells counted. This case, however, was classified as the secondary type and made no response to liver extract, but responded rapidly to 100 grains of iron daily. The white count was below 8,000 in fifteen, and ranged between 8,000 and 20,000 in the others.

Five of the cases gave histories of recurrence, two more were treated for the initial attacks and later the recurrence in the hospital. In each instance the recurrence occurred with pregnancy. The youngest gave the age of 16, and the oldest 38, average for the twenty-two, 26 years. The absence of recurrence except with the pregnancy, and the youth of the patients are distinctly against the findings in pernicious, or true Addisonian anemia.

Thirteen received transfusion. Of these two died. One of these was extremely ill on admission, and died thirty hours after transfusion with

acute dilatation of the heart. The second of the transfused series to die, did not follow up treatment. The third case to die, was not transfused for lack of a suitable donor, left the hospital and refused treatment. Six made a complete recovery on liver extract alone. One did not improve on liver, but made rapid progress on 100 grains of Bland's mass daily.

The following cases are presented as typical of the anemia, with the added features of being very severe, not responding to transfusion, but to liver extract.

Mrs J. A. S., Hosp. No. 15,439, age 33, para V, admitted to the hospital January 4th, 1928, with the complaints of weakness, dyspnea, dizziness, and headaches.

She had noticed these symptoms for a month and a half before her baby was born. On admission, her baby was 10 days old, and her former complaints had been aggravated since its birth.

She had had high blood pressure and severe nephritis with her fourth baby. She had had three miscarriages, and one baby died at the age of two years. As a child she had had "rheumatism" and typhoid fever, but no other illnesses save child-births.

On examination she appeared well nourished, but very anemic. Her eye-grounds showed recent retinal hemorrhage. There were no cardiac murmurs, no cardiac enlargement. Her blood pressure was 130-90, pulse 100, temperature 102. The liver and spleen were both palpable. The tendon reflexes were normal, no Babinski. The uterus showed moderate subinvolution, with slight stellate tears of the cervix.

Laboratory findings. Urine, albumin 11 on a scale of 14, many hyaline, granular, and cell casts. Blood hb 20%, red cell count 1,060,000, white cell count 16,400, polymorphonuclears 86%, lymphocytes 11%, transitionals 2%, eosinophiles 1%. The platelets were estimated as plentiful. There was marked difference in size and shape of the red cells, marked achromia, no malaria,

marked stippling and polychromatophilia. The icterus index was 20, Van den Bergh direct reaction, hemolysis of the red cells began at 0.4 and ended at 0.275. The blood urea was 32 mg, blood Wassermann negative. The feces showed no hook-worm ova, the gastric contents showed no free hydrochloric acid.

On January 6th, she was transfused with 500 cc of citrated blood with no reaction. On January 12th, the day she left the hospital, her red cell count was 1,890,000, hb 40%, white cell count 9,400, polymorphonuclears 78%, lymphocytes 6%, large mononuclears 14%, transitionals 1%, eosinophiles 1%. Anisocytosis and poikilocytosis marked.

She was given dilute hydrochloric acid and liver feedings which she refused. Soon after leaving the hospital, she lost the gain she had made. Her vision became very much impaired and she developed a generalized edema. It was felt that she had not received sufficient benefit from the transfusion to repeat it. She was then put on liver extract which she tolerated better than the liver feeding. Improvement on this was very rapid. The vision improved, but never returned to normal. On April 3rd, 1930, her red cell count was 4,210,000, hb 80%, smear showed normal red cells.

A second case of interest is case 214 in our series. Mrs. A. T. G. who was treated twice for the same condition. Was age 22 when first seen in July, 1926, at which time she complained of weakness. She was pregnant and nearly at term. General physical examination was practically negative except for the apparent marked anemia. She had 1,050,000 red cells and hb 25% blood Wassermann negative. Her stools contained hook-worm ova. Her temperature was 102, white count 5000 with a normal differential (no increase in eosinophiles) urine contained albumin II on a scale of IV. She was transfused with 500 cc of citrated blood and given two treatments for her hook-worm and put on dram doses of dilute hydrochloric acid. She went to term and delivered a normal baby that is still living. She then got along alright at home until two months before her second admission in August 1928. She was delivered of her fifth baby two months before admission and although she lost very little blood she was compelled to

get weak and pale. She was sent to us again for transfusion. This time her skin had a slightly yellowish appearance (icterus index 22) but her general physical examination was essentially negative. She was nursing her baby. Her red cell count this time was 1,350,000, with hb 30%, and blood volume index 119. There was definite change in size and shape of the red cells. Her Wassermann was negative again and the stools repeatedly negative. Her hydrochloric acid was 12. The urine showed an albumin I on a scale of IV. Her blood urea was 40 mg per 100 cc and kidney function 69% in two hours. Although she was fairly sick there was no emergency so we decided to try liver extract instead of transfusion. She was given one ampule of Lilly's Extract 23.43 after each meal. At the sixth day her red count was 2,160,000 and hb 45%. Her appearance and feelings were much improved. On the 12th day her count was 2,460,000 and hb 50%. The patient continued to improve at home and since then has had another baby, and her physician, Dr. Julian Brantley, of Spring Hope, N. C., stated recently that she was not anemic and had no trouble with her last pregnancy.

### Discussion

While we find that many of these cases resemble pernicious anemia very closely, there are many that do not, and yet the anemia is definitely associated with pregnancy and the puerperium. We are not able to agree with Alder<sup>6</sup> who states flatly "that in the history of almost every instance of the pernicious type of the anemia of pregnancy there occurs a reference to some previous chlorosis, severe anemia, syphilis, or other infection." McSwiney<sup>7</sup> in analyzing 43 cases of various types of anemia of pregnancy was impressed with the frequent association of syphilis with the anemia. Eighteen of our patients had negative Wassermanns (Kolmer) and the test was positive on the other four.

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### Discussion

While we find that many of these cases resemble pernicious anemia very closely, there are many that do not, and yet the anemia is definitely associated with pregnancy and the puerperium. We are not able to agree with Alder<sup>8</sup> who states flatly "that in the history of almost every instance of the pernicious type of the anemia of pregnancy there occurs a reference to some previous chlorosis, severe anemia, syphilis, or other infection." McSwiney<sup>9</sup> in analyzing 43 cases of various types of anemia of pregnancy was impressed with the frequent association of syphilis with the anemia. Eighteen of our patients had negative Wassermans, (Kolmer) and the test was not made on the other four.



Aubertin<sup>10</sup> does not hesitate to call the condition pernicious anemia, and Brady<sup>11</sup> who collected 68 cases from various sources, and others, do not hesitate to term the condition "Pernicious anemia of pregnancy," however, we have not been able to find any case in the literature that meets the modern requirements for a diagnosis of typical Addisonian anemia. The etiology is obscure, and the disease is pernicious in most cases unless checked, however, one very important fact is that when recovery takes place it is permanent, with no remission and no recurrence unless at a subsequent pregnancy which does not necessarily follow, and therefore an attack successfully treated is not a contraindication to subsequent pregnancies.

We feel that the term "pernicious anemia" is loosely used, less obnoxious would probably be "A pernicious type of anemia," however, in the secondary type the patient may also have a fatal termination if not properly treated.

Unless puerperal anemia is kept in mind, the patient in almost every instance will be treated for some other complication. In our series, the red counts were so low, that the most ob-

vious need of the patient was blood. Our early cases were all transfused provided a suitable donor could be found but in no instances did we rely on transfusion alone, although Allan<sup>12</sup> states that transfusion alone is curative. Knowing that transfusion is not always available and following its failure in some instances to give the desired result (case 7 and 17 of this series) we have utilized liver extract in selected cases. As stated above, transfusion may be a life saving measure, but we hope that with the early recognition of the disease that liver extract or iron may be used before the condition of the patient gets so serious as to require transfusion. We had six to make a complete recovery on liver extract alone. In the literature liver extract has been used successfully by Brault<sup>13</sup>, Larribere<sup>14</sup>, Peterson<sup>15</sup> and others.

In conclusion we believe that there is an anemia of pregnancy and the puerperium that is a definite clinical entity. That in some instances it closely resembles pernicious anemia but not true Addisonian anemia. The indications for treatment are definite and the response is very satisfactory.

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# Variations in Pulse and Blood Pressure With Interrupted Change of Posture\*

By DAVID G. GHRIST, M.D., *Fellow in Medicine, The Mayo Foundation, Rochester, Minnesota*

CAREFUL studies of the normal circulatory response to uninterrupted changes of posture from recumbency to standing have been previously reported<sup>4,5,6</sup>. Following Ghrist and Brown's report of a step-like fall of both systolic and diastolic blood pressure, with associated faintness or syncope on passive, interrupted change of posture from recumbency to standing in one case of postural hypotension with syncope and in one case of proved Addison's disease, it was deemed advisable to repeat these fractional postural studies on groups of normal subjects and of patients. The following study of pulse rate, blood pressure and resultant symptoms from passive postural change, both interrupted (in all persons) and uninterrupted (in thirty-two of the entire number), represents observations carried out on forty normal persons (twenty-three females and seventeen males) and on 108 registered patients at The Mayo Clinic and its allied hospitals. The mean results of all these determinations are presented in the accompanying table. The normal persons studied were mainly of three occupations: physicians, technicians and secretaries. The conditions of the patients chosen for study are classified in the following

main groups: (1) hypotension, systolic blood pressures of 100 mm of mercury or less, (2) benign (essential) hypertension, systolic blood pressures of 140 mm or more, (3) malignant (essential) hypertension, (4) postural hypotension with syncope, (5) postural weakness or dizziness, (6) diabetes mellitus, (7) nonpostural weakness or dizziness, (8) Addison's disease, (9) chronic infectious arthritis<sup>†</sup>, (10) Raynaud's disease,<sup>†</sup> and (11) scleroderma. When individual cases were included in more than one group, this is indicated.

## METHOD

All determinations of pulse and blood pressure were carried out by me, over a period of thirty-three months, in the same room, at hours varying from 11 a.m. to 8 p.m. The subjects were made to lie horizontally on a roentgenographic table (180°) for periods of from three to fifteen minutes, until two consecutive readings of

\*\*Abridgement of thesis submitted to the Faculty of the Graduate School of the University of Minnesota in partial fulfillment of the requirements for the degree of Master of Science in Medicine 1930.

<sup>†</sup>Certain of these were studied before and after sympathetic ganglionectomy and trunk resection.

blood pressure fell within 2 mm of each other, in both systolic and diastolic levels. An upright mercury standard type of blood pressure apparatus was used in all determinations, with the cuff applied to the upper part of the right arm of the subject and the calibrated mercury scale standing at the approximate level of the subject studied. The mechanism was explained to the subjects before the test was begun in order to reduce the element of apprehension to a minimum. After the blood pressure had agreed within 2 mm (both systolic and diastolic) the pulse was determined for fifteen seconds and the last reading of blood pressure and the associated pulse rate were recorded. The subject was then moved to posture 2 ( $157.5^\circ$ ) by use of the electric motor attached to the table. Determinations of blood pressure and pulse rate were then taken at the new posture. The same procedure was carried out at  $135^\circ$ ,  $112.5^\circ$  and  $90^\circ$ \* (erect) in sequence as indicated. The time elapsing between determinations at posture 1 and posture 5 averaged about five and a half minutes.

When uninterrupted determinations of pulse and blood pressure were made, the same general procedure was carried out, with the exception that the motor, and motion of the table, were not allowed to stop between postures 1 and 5. The time elapsing between determinations at posture 1 and at posture 5 was approximately two minutes in the uninterrupted tests. The mean

average results in the groups studied are presented in the tabulation.

#### COMMENTS AND CONSIDERATION OF RESULTS

The average normal circulatory responses to passive change from recumbency to the erect posture are (1) rise of pulse rate, (2) rise of diastolic blood pressure (a probable index of vasomotor tonus), and (3) slight fall or stationary maintenance of the systolic blood pressure (fig. 1). The mechanisms by which these effects are accomplished are as follows: (1) decrease of the venous return incites the cardiac mechanism to increased rate in order to maintain equality of cardiac output in the upright posture, and (2) through the agency of vasomotor stimulation, a vasopressor response takes place in the peripheral circulation (splanchnic area especially) to oppose the hydrostatic effect of gravity, and to maintain sufficient diastolic level to preclude anemia of the brain. Defective vasomotor tonus may arise from (1) paralysis, inhibition or dysfunction in the nervous mechanism of vasomotor control, which in turn is influenced by the circulating hormones of glandular secretion, (2) atony or paralysis of the myoneural junction in the peripheral (especially splanchnic) vessels, or (3) changes in the character of the walls of the blood vessels themselves. Some compensation for these defects may or may not be obtained by tonus of abdominal muscles and increase of respiratory movements which oppose splanchnic congestion and facilitate venous return.

In the course of interrupted, passive change from recumbency to the erect

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\*The more exact angle of the erect posture with the table used measured  $93^\circ$ . For the purpose of clarity, the approximate figure,  $90^\circ$ , will be used in the tables, graphs, and so forth.

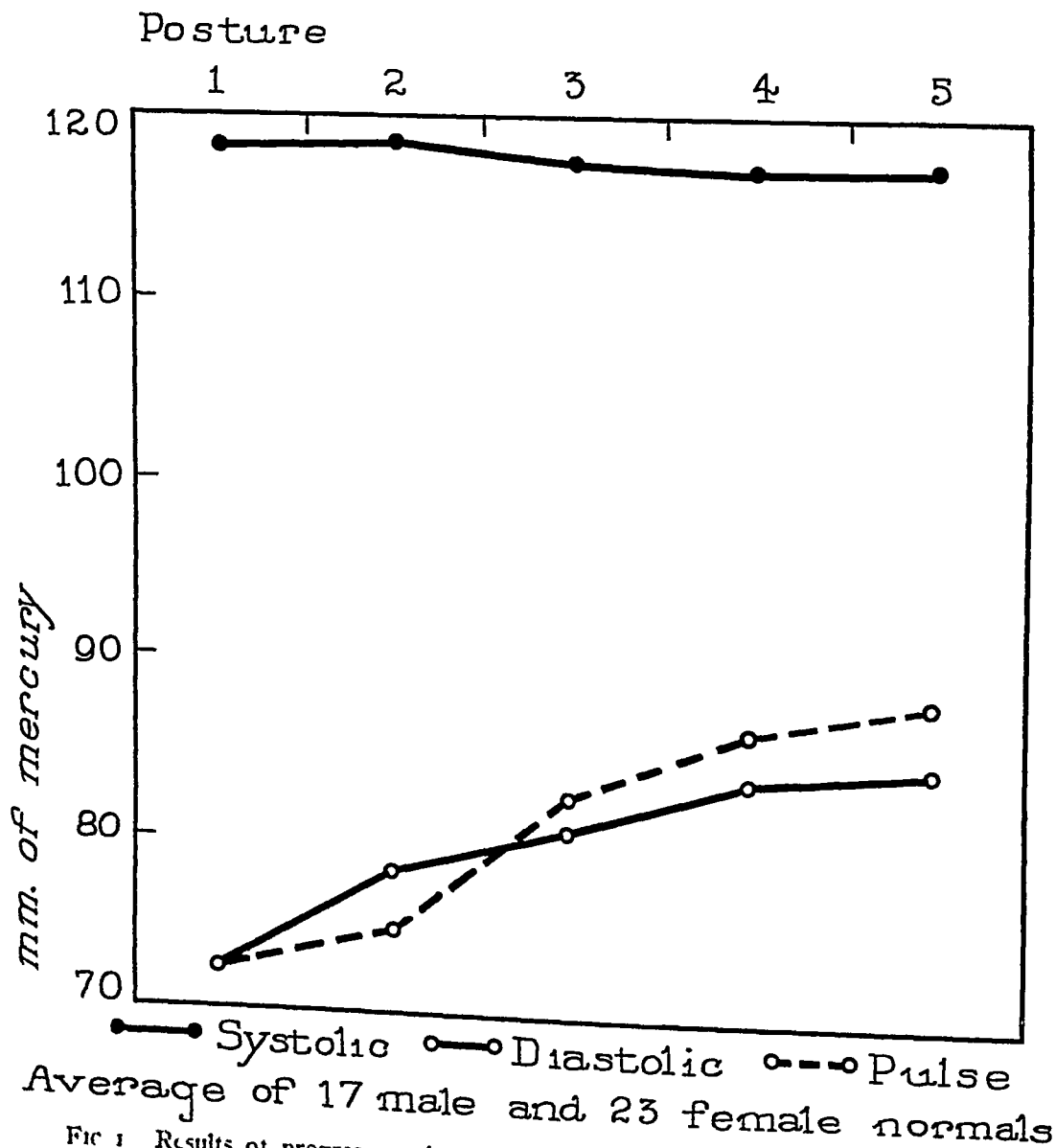


FIG 1 Results of progressive change in posture of normal subjects, seventeen males and twenty-three females. The postures are designated as follows (1) supine or  $180^{\circ}$ , (2)  $157.5^{\circ}$ , (3)  $135^{\circ}$ , (4)  $112.5^{\circ}$ , and (5) erect or  $90^{\circ}$ .

position, from which the following estimations of the average normal response were made, the pulse should rise approximately fifteen beats each minute, the systolic blood pressure should remain approximately unchanged (average fall 1 mm) and the diastolic pressure should rise approximately 12 mm in a group of normal adults aged approximately twenty-seven and two-tenths years. Individual normal subjects may vary considerably above or below these average determinations. No pertinent fall of diastolic blood pressure took place during any of the determinations on normal subjects, although three of these subjects exhibited falls of 4.2 and 2 mm of diastolic blood pressure, respectively. The presence of definite hypotension, along with undernourishment, did not preclude approximately normal response of blood pressure to passive postural change in the group of eleven such cases studied.

A representative group of twenty cases of benign (essential) hypertension (fig 2) exhibited instability of systolic blood pressure on postural change, which appears to indicate the presence of remaining flexibility in the peripheral resistance at high pressures. The same persons reacted with subnormal rise of diastolic pressure on postural change, which gives evidence of pre-existent vasospasm or inelasticity, or both, in the peripheral vascular system.

The ten cases of malignant (essential) hypertension (fig 3) as a group gave evidence of less flexibility in the peripheral vascular system than the cases of benign hypertension. The reactions in these cases yielded physiologic evidence of severe, inflexible

arteriolar constriction, corroborating the previous contentions of Keimohan, Anderson and Keith. Also, the circulatory adjustment of these patients to postural change is accomplished with less rise of pulse rate than in those who are normal or who have benign hypertension. This has two possible explanations: the struggle of the circulatory mechanism against its severe basal load and cardiac hypertrophy of such magnitude as to accomplish slight physiologic adjustment with less change of rate, provided cardiac reserve is relatively adequate\*.

On postural test the series of six cases in which there was generalized (senile) arteriosclerosis gave evidence of less peripheral flexibility and less vasomotor tonus than the group with benign hypertension.

There was marked fall of systolic and diastolic blood pressure with unchanging pulse rate in Ghist and Brown's previously reported case of postural hypotension with syncope. In their case, evidently atony in the myoneural juncture of the splanchnic arterioles was the main cause of failure in the mechanism of vasomotor tonus. Successful treatment of the patient by repeated doses of ephedrine gave striking corroboration of the above contention.

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\*Seven of these cases in which the electrocardiograms were significant of myocardial degeneration gave evidence that instability of their systolic blood pressure cannot be explained on the basis of a defective myocardium. The failure of the diastolic blood pressure to rise on postural change also was not confined entirely to those cases in which there was electrocardiographic evidence of myocardial degeneration.

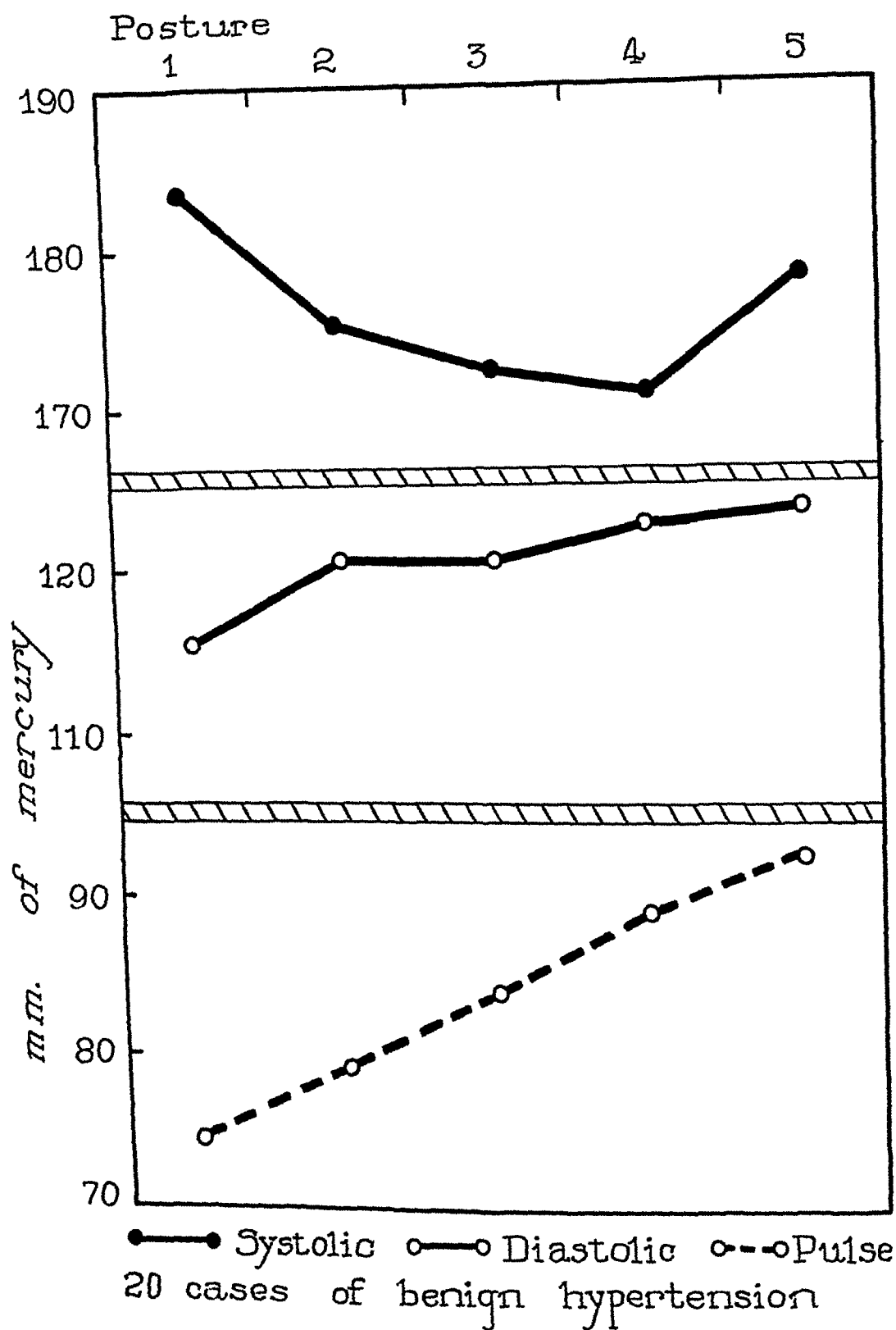


FIG. 2 Results of progressive change in posture of twenty patients with benign hypertension

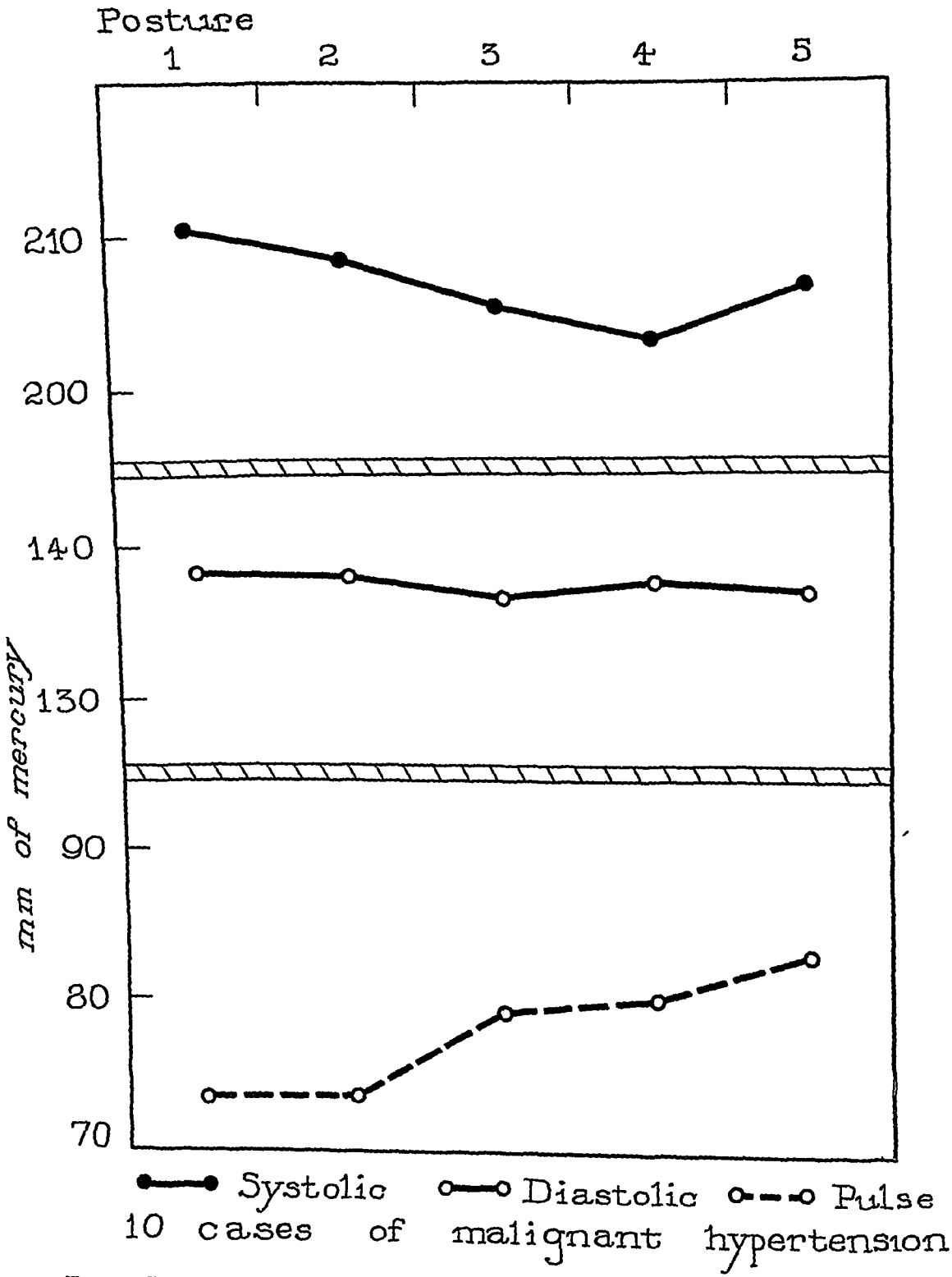


FIG 3 Results of progressive change in posture of ten patients with malignant hypertension

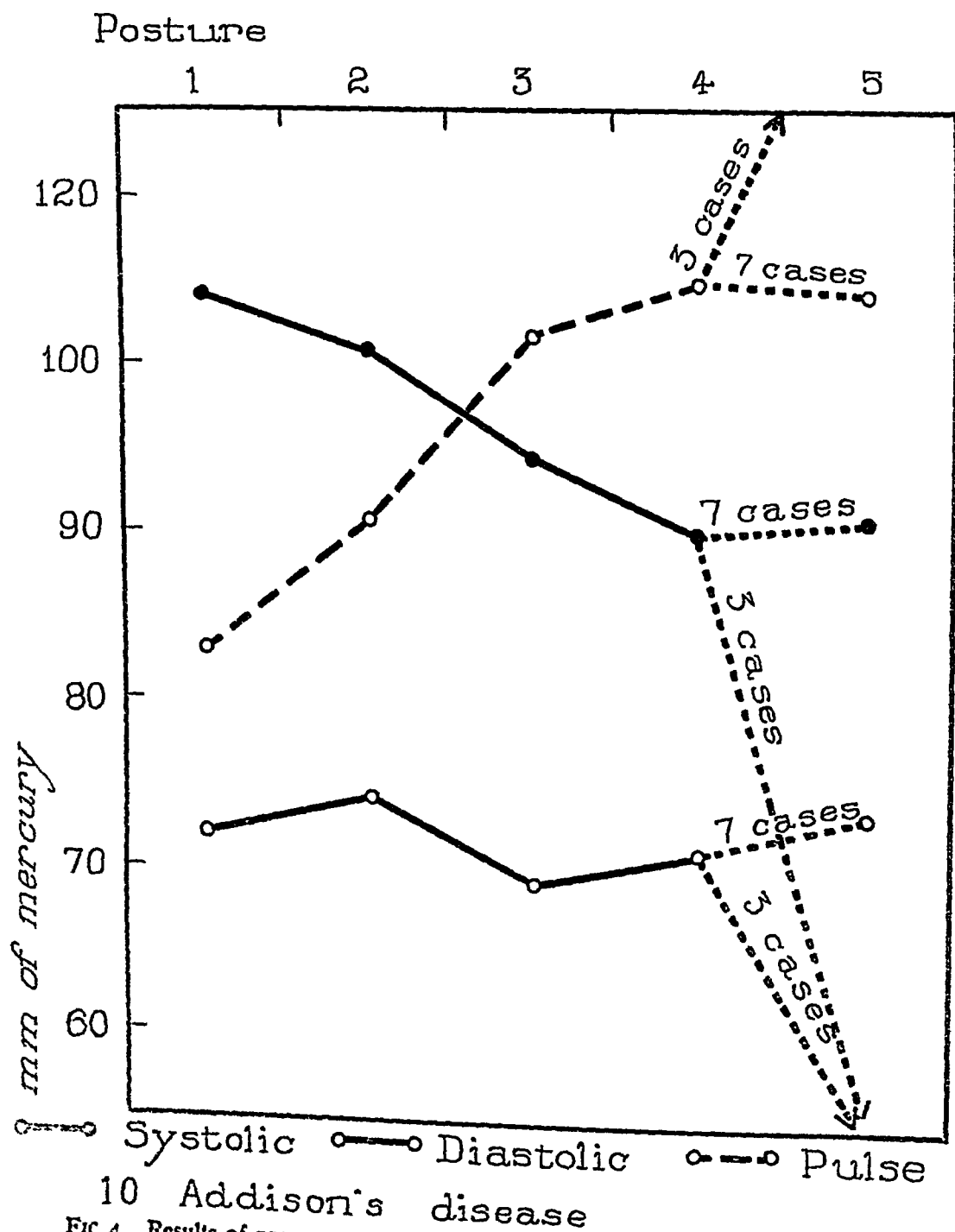


FIG 4 Results of progressive change in posture of ten patients with Addison's disease.



In approximately 50 per cent of cases of diabetes mellitus, a history of weakness, dizziness or faintness on changing from a lying or sitting to a standing position can be elicited. Three of the thirteen patients with diabetes, who had a history of symptoms due to posture, exhibited these symptoms at posture 5 of the interrupted postural test. All patients with diabetes lacked stability in systolic blood pressure on postural test. Lack of normal vasopressor response also was seen in the group with diabetes. The explanation of this feature seems to lie in the factors of senile changes in the walls of the peripheral vessels, in the general weakness,<sup>†</sup> contributing to decrease of vasomotor tonus, and in the possible element of vasospasm present even under basal conditions. The senile arterial and arteriolar changes seem more important than either of the other possible factors of decreased vasomotor tonus in diabetic persons.

Of seventeen persons who did not have diabetes, but who were noticeably underweight and who had a history of symptoms of changing posture, five experienced weakness or dizziness at posture 5 in the interrupted postural test.<sup>†</sup> The postural reactions of these patients gave evidence of more marked deficiency in vasomotor tonus than those of other patients in the same group who were also deficient in vasomotor tonus. The systolic instability

of these five patients outdid the same tendency in others of the same group. These observations give evidence that circulatory inefficiency on postural change was a definite factor in the postural symptoms of these patients.

In cases of weakness not associated with change of posture, symptoms were not produced by the postural test. This indicates that few complaints of general weakness are associated with significant circulatory deficiency on postural change unless a history of this relationship is elicited from the patient. This group gave evidence of normal activity of vasomotor tonus up to the last positions of the interrupted postural test, apparently, the interrupted type of test is of value in showing what evidently represents a fatigue element after three to four minutes of utilization of the vasomotor mechanism for postural adjustment. Inclusion of the pertinent cases of diabetes mellitus with the other cases in which there was a history of postural symptoms, brings out the fact that among these thirty-two patients, 25 per cent experienced weakness or faintness from undergoing the interrupted postural test\*.

Conservative estimate of the incidence of severe circulatory embarrassment on interrupted postural change indicated that in 30 per cent of the ten patients with Addison's disease, the levels of systolic and diastolic blood pressure were approaching those of syncope when posture 5 was reached (tabulation and fig. 4). Two other patients (20 per cent) suffered definite

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<sup>†</sup>The strength of more than 50 per cent of the patients who had diabetes mellitus was less than normal.

\*\*A correlation of the presence or absence of anemia in all groups revealed no relationship between deficient circulatory response and anemia.

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\*Inclusion of Addison's disease and postural hypotension with syncope would appreciably raise the percentage incidence of symptoms during the postural test.

symptoms of circulatory embarrassment of posture 5 Fifty per cent of the patients either were under, or within thirty-six hours had been under the Muirhead regimen Thus, the reactions of the patients should be taken conservatively in estimating the reactions of an untreated group of patients with Addison's disease The striking failure of circulatory adjustment to posture which these persons exhibited, apparently arose from a combination of factors Some of these factors were decreased size of the heart, failure of vasopressor adjustment, with shift of the mass of blood to the capillaries, venules and venous regions of the splanchnic circulation, general muscular weakness and atony which probably augmented inefficient venous return, and defective tonus of the walls of the blood vessels Decrease or abnormality of circulating hormone from the suprarenal glands probably is a major factor in these abnormal reactions during passive postural change

Subnormal vasopressor response to postural change, exhibited in cases of chronic infectious arthritis, corroborates previous work of myself in which decreased vasopressor reaction to stress and strain was exhibited by these patients The rise of both systolic and diastolic blood pressure at posture 1, following performance of lumbar sympathetic ganglionectomy and trunk resection after the method of Adson, argues for compensatory augmentation of tonus in regions which have not been released from sympathetic control The nonreleased splanchnic region of the patients who have undergone lumbar ganglionectomy and trunk

resection continues to adjust as formerly, for postural change.

The two cases of Raynaud's disease exhibited little deviation from normal postural response except for instability of the systolic pressure, which might be expected. Cervicothoracic sympathetic ganglionectomy and trunk resection in these cases may slightly reduce the blood pressure in the region of the brachial artery by relaxing the vessels in the regions released from sympathetic control The systolic instability shown preoperatively is absent postoperatively No appreciable change in the reactions of diastolic blood pressure occurred following ganglionectomy and trunk resection

The normal response of systolic blood pressure to postural change in four cases of scleroderma indicates stability of peripheral vascular resistance Lack of vasopressor response, as indicated by relatively fixed diastolic pressure in all postures, seems best explained on the basis of vascular spasm, thickening of the vascular walls, and perivascular infiltration in the skin or surface areas These conditions seem to be compensated for by relative relaxation of the splanchnic circulatory apparatus Normal response to postural change in one of these cases following lumbar sympathetic ganglionectomy lends logic to this contention

Correlation of the reactions to both interrupted and uninterrupted tests shows the following discrepancies in the results from the two types of passive change from the recumbent to the erect posture. slightly greater average fall of systolic and slightly greater average rise of diastolic blood pressure

obtains from the interrupted postural test, and slightly greater average rise of pulse rate obtains in the uninterrupted test. Since, in the interrupted test, approximately three minutes longer are available for circulatory adjustment than are available in the uninterrupted test, the readings at posture 5 in the interrupted test should give better qualitative and quantitative estimation of physiologic response than the uninterrupted test.

#### SUMMARY AND CONCLUSIONS

1 Fractional determinations of blood pressure, pulse, and symptoms, on passive change from recumbency to the erect posture, yield information as to pathologic physiology involving the circulatory apparatus in groups of cases in which disturbances of this type are suspected.

2 The incidence of normal response in many of the persons who comprise pathologic groups and vice versa make single determinations of little scientific value, except when the deficiency of circulatory adjustment is severe.

3 Neither hypotension nor undernourishment precludes normal response of the circulatory apparatus to passive change from recumbency to standing.

4 Patients with scleroderma, chronic infectious arthritis, and benign (essential) hypertension, taken as groups, exhibit subnormal rise of diastolic blood pressure on passive change from recumbency to standing, whereas patients with malignant (essential) hypertension taken as a group exhibit fixation of diastolic blood pressure during the same procedure.

5 The highest incidence of signs or symptoms of weakness, faintness or dizziness, on passive change from recumbency to standing, was found in groups of patients from whom a history of postural symptoms could be elicited.

6 Correlation, during the above postural tests, of inefficient circulatory adjustment, with the history of postural symptoms before the tests were performed, is possible in a certain proportion of cases.

7 Groups of patients diagnosed postural hypotension with syncope, Addison's disease, diabetes mellitus, and asthenia, present the highest percentage of correlation in the phenomena mentioned in the two previous sentences.

8 Patients with nonpostural weakness initiate normal circulatory adjustment to passive postural change but show evidence of fatigue in its maintenance.

9 Neither lumbar nor cervicothoracic sympathetic ganglionectomy and trunk resection appears appreciably to alter the manifestations of vasomotor tonus expressed by diastolic rise of blood pressure on change from recumbency to standing in cases of chronic infectious arthritis and Raynaud's disease.

10 Interrupted determination of postural adjustment by the circulatory mechanism yields results that can be seen in alterations of the same phenomena as those affected in the uninterrupted procedure, and, in addition, the interrupted method affords more qualitative and quantitative information.

GROUP STUDIES OF PULSE RATE BLOOD PRESSURE AND SYMPTOMS DURING PASSIVE POSTURAL CHANGE

Group studied	Posture*	Average blood pressure				Symptoms, of dizziness, weakness or faintness	Average age, years	Average weight
		Average pulse rate	Systolic	Diastolic				
Normal (23 women and 17 men)	1	72.6	118.5	72.3	Two women slightly faint at posture 5**		27.2	Approximately normal
	2	74.8	118.7	78.0				
	3	82.4	117.7	80.6				
	4	86.0	117.2	83.5				
	5	88.0	117.5	84.6				
Hypotension (systolic blood pressure 100 mm or less) 11 cases	1	69.0	91.6	60.2	None		41.3	Underweight, 17 pounds
	2	74.9	91.8	61.5				
	3	78.4	92.2	66.2				
	4	83.4	91.8	67.9				
	5	87.8	91.3	70.0				
Benign (essential) hypertension, 20 cases	1	74.1	183.2	115.4	None		43	Overweight, 31 pounds
	2	79.0	175.0	120.3				
	3	83.9	172.1	120.6				
	4	88.8	170.8	122.7				
	5	92.1	177.8	123.4				
Malignant (essential) hypertension, 10 cases	1	73.2	210.4	138.2	None		44.6	Overweight, 1 pound
	2	73.7	208.8	138.0				
	3	79.3	205.4	136.6				
	4	80.1	203.4	137.4				
	5	83.2	207.0	136.0				
Generalized (semile) arteriosclerosis, 6 cases	1	78.6	150.0	89.0	None		59.3	Approximately normal
	2	81.5	147.0	91.6				
	3	84.8	144.5	90.0				
	4	91.0	142.8	95.3				
	5	94.7	147.0	96.6				
Postural hypotension and syncope, 1 case	1	84.0	128.0	98.0	Severe faintness and syncope at posture 5		41	Overweight, 5 pounds
	2	86.0	106.0	74.0				
	3	84.0	82.0	52.0				
	4	84.0	78.0	40.0				
	5	80.0	54.0	40.0				

Histories of postural symptoms before test *** 32 cases					Slight to moderate, 8 cases	44 2	Underweight, 5 4 pounds
Diabetes mellitus, 19 cases					Moderate, 3 cases	44 7	Underweight, 2 pounds
1	80 3	124 4	82 4	83 3			
2	86 2	121 5	83 3	83 9			
3	89 9	117 9	81 4	81 4			
4	95 6	115 1	83 9	83 9			
5	99 2	115 9					
Nonpostural weakness, 15 cases					None	49 6	Underweight, 14 6 pounds
1	72 3	104 1	71 3	75 6			
2	77 5	104 0	78 3	78 3			
3	83 6	101 7	78 3	78 3			
4	87 2	101 7	76 9	76 9			
5	93 3	102 9					
Addison's disease, 10 cases					Definite, 2 cases, severe, 3 cases	39 6	Underweight, 13 5 pounds
1	83 0	104 0	72 0	74 2			
2	91 6	100 8	69 2	Below			
3	101 6	94 4	Below	71 1			
4	Above	90 0	Below	Below			
5	104 0	Below	73 5				
Chronic infectious arthritis, 9 cases					None	35 5	Approximately normal
1	86 7	108 2	70 4	73 4			
2	89 3	104 7	76 2	76 2			
3	94 2	103 1	76 2	76 2			
4	98 0	101 6	78 0	78 0			
5	102 0	104 9					
Chronic infectious arthritis (5 of the 9 cases)					None		
1	93 7	103 7	66 8	71 5			
2	96 0	102 6	72 0	73 4			
3	100 4	103 4	77 3	77 3			
4	109 0	100 0					
5	108 6	108 2					
After lumbar sympathetic ganglion-ectomy and trunk resection							
1	92 8	108 4	70 8	75 2			
2	99 2	105 2	72 0	76 8			
3	112 8	104 8	81 6				
4	118 0	104 8					
5	122 0	109 2					

Group Studies of Pulse Rate Blood Pressure and Symptoms During Passive Postural Change—Continued

Group studied	Posture*	Average blood pressure			Symptoms of dizziness, weakness or faintness	Average age, years	Average weight
		Average pulse rate	Systolic	Diastolic			
Before operation	1	78.0	118.0	75.0		29.5	Underweight, 185 pounds
	2	80.0	111.0	79.0			
	3	88.0	112.0	80.0			
	4	91.0	115.0	80.0			
	5	88.0	116.0	84.0	None		
Raynaud's disease, 2 cases	1	88.0	112.0	69.0			
	2	88.0	111.0	71.0			
	3	92.0	111.0	77.0			
	4	96.0	110.0	81.0			
	5	96.0	113.0	76.0			
Scleroderma, 4 cases	1	80.0	113.5	72.5	None	36.2	Underweight, 265 pounds
	2	84.5	112.5	74.0			
	3	88.0	112.0	78.5			
	4	91.0	109.5	76.7			
	5	94.0	112.0	74.5			
Comparison of interrupted and uninterrupted methods, 32 cases	1	76.1	127.2	83.1	None		
	5	90.7	125.0	91.8			
	1	75.1	126.4	83.2			
	5	91.2	125.1	89.2			

\* Posture 1 = 180° (horizontal)

Posture 2 = 157.5°

Posture 3 = 135°

Posture 4 = 112.5°

Posture 5 = 90° (erect)

\*\* One of these had phobia for blood pressure determinations and the other was tested during menses

\*\*\* Cases of Addison's disease and of postural hypotension with syncope excluded from this group, whereas thirteen cases of diabetes mellitus are included

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- <sup>2</sup>CHRIST, D G The temperature of the upper and lower extremities in relation to the control exercised by the sympathetic nervous system *Proc Staff Meetings of Mayo Clinic*, 5 25-26 (Jan 29) 1930
- <sup>3</sup>CHRIST, D G and BROWN, G E Postural hypotension with syncope, its successful treatment with ephedrine *Am. Jour Med. Sc*, 175 336-349 (March) 1928
- <sup>4</sup>HILL, LEONARD and BARNARD, HAROLD The influence of the force of gravity on the circulation Part II. *Jour Physiol*, 21. 323-352 (May) 1897.
- <sup>5</sup>KERNOHAN, J. W, ANDERSON, E. W and KEITH, N. M The arterioles in cases of hypertension *Arch Int Med*, 44 395-423 (Sept) 1929.
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# Venous Pressure in Pneumonia\*

By GEORGE J KASTLIN, M D , and W W G MACLACHLAN, M D ,  
*Pittsburgh, Pa*

**I**N THE study of the circulation in the normal individual, Eyster, Hooker, Clark and others have placed particular emphasis on the variations and importance of the venous pressure. The results of these investigations have given evidence that the venous pressure is altered greatly by varied demands on the circulatory mechanism. It has been observed that the venous return of blood to the heart apparently regulates in large part the arterial output. The venous pressure determines the degree of filling of the ventricular chambers in diastole, and this determines the amount of blood expelled at each contraction of the ventricles. An increased venous pressure, therefore, results in an increase in the amount of blood pumped into the arterial system. The normal heart responds to an increased venous pressure by increased output, and furthermore, is able to react favorably to great variations in pressure.

This physiological conception of venous pressure has been applied to the study of cardiac disease and especially in recent years its value as an aid in the clinic has been emphasized by Eyster and Middleton<sup>1,2,3,4</sup>. Eyster<sup>4</sup>

(page 117) states that, "the condition in which the venous load exceeds the capacity of the heart to respond by increased output into the arterial system or in which the heart fails to move the blood adequately from the venous to the arterial side, is called cardiac decompensation or cardiac failure". Observations in cases of cardiac failure have shown that the increase of venous pressure is proportionate to the degree of cardiac failure, and may be used as a clinical guide of this condition. Venous pressure studies have been applied to the various types of organic heart disease and to conditions in which the heart is affected secondarily as a result of toxemia. From his clinical observations on venous pressure Eyster<sup>4</sup> (page 117) further states, "cardiac decompensation occurs only in the presence of heart muscle injury, either (and most frequently) as a result of degenerative processes superimposed on muscle hypertrophy, or as a result of toxemia (associated with pneumonia and more rarely other acute infections)".

Analysis of the few reported cases of lobar pneumonia with venous pressure observations indicates that in a small proportion of the cases the venous pressure was increased at some time during the infection. Schott,<sup>5</sup> in

\*From the Medical Clinic of Mercy Hospital, Pittsburgh, and Department of Medicine, University of Pittsburgh.



1912 reported 4 cases, all with normal venous pressure. Fuchs,<sup>9</sup> in 1929, reported 9 cases, 8 of this group maintained a normal venous pressure, with 2 fatal cases included. The remaining case had a normal venous pressure at the onset but developed signs of cardiac decompensation and an increase of venous pressure to 17.3 cm on the third day. Venesection decreased this pressure to 13.5 cm but the patient died on the fourth day. Eyster and Middleton,<sup>1</sup> in 1924 reported 8 cases. 6 of these had a normal venous pressure throughout the illness and showed no evidence of cardiac failure. 2 cases, with evidence of cardiac failure, showed a high venous pressure, one of which had two periods of increased pressure and ultimately recovered. These authors noted that a rising venous pressure and capillary stasis preceded the clinical evidence of cardiac failure.

We have had the opportunity of observing a number of cases of pneumonia in which venous pressure data have been collected. This report is composed of cases in the first two years of our work. The infection in this community is severe and has a subsequent high mortality. The cause of death in pneumonia has usually been attributed to cardiac or respiratory failure. We have been impressed from clinical observation with these possibilities but have been doubtful as to our ability to recognize signs of congestive heart failure in a patient seriously ill with pneumonia. We were therefore interested in venous pressure observations, particularly in the severe forms of the disease, and have been impressed by the value of these obser-

vations as an index of the state of the circulation. Further we have utilized venous pressure as a guide to intravenous dextrose medication in cases of pneumonia recently reported by us<sup>10</sup>

#### MATERIALS AND METHODS

Ninety cases of pneumonia are reported as seen in hospital practice. We include under the term pneumonia the lobar and the bronchial forms, much of the infection in this community is of the latter type. Post-operative pneumonia and the infection in children are not included. The cases are divided into two groups to facilitate their study. Group "A" includes cases receiving the usual treatment for pneumonia, while Group "B" had intravenous dextrose therapy in addition.

The indirect method of determining venous pressure with the simple or compensating "U" tube water manometer was used, as described by Hooker and Eyster.<sup>7</sup> A portable instrument modified by one of us (Kastlin) was found to be most useful. An obsolete model of Faught "U" tube sphygmomanometer was converted into a venous pressure manometer by replacing the mercury with water. The two outlets of the manometer were used, one to the bulb, the other to the glass-top air chamber. The millimeter scale is adaptable to centimeters and is movable, to be readily adjusted to the fluid level in the tube which varies by evaporation, et cetera. The "U" tube instrument, in our experience, is easier to operate than the type with the tube and reservoir because of the ease of holding the compensated column of fluid steady while making the reading.

All readings were made by one of us and were made daily or oftener. The same prominent vein on the back of the hand was used in successive readings in each case. The patients were all recumbent and at rest, the vein held at cardiac level, which was taken as one-third of the distance from the anterior surface of the thorax to the dorsal surface at the level of the fourth intercostal space. The minimum pressure producing compression of the vein was accepted as the reading. Co-ordination between the hand holding the air chamber in contact with the skin and the hand applying pressure to the bulb is necessary to obtain consistent readings. Frequently the patient's hand must be shaved to obtain good vision of the vein. By perfection in technique, readings may be taken on small veins and on veins constricted by venomotor activity. In only one instance was observation impossible because of extreme thickness of the skin of the hands and over other peripheral veins. The above method insured uniform conditions for the taking of records as recommended by Eyster.

The normal venous pressure was considered to be any reading of 11 cm of water or lower (Eyster and Middleton<sup>1</sup>). Cases with pressures of 12 cm to 16 cm were tabulated as slightly elevated. Elevation of 17 cm or more of water was considered high or critical (Clark)<sup>2</sup>.

## DATA

### Group A (Cases receiving usual treatment)

Total number	50
1 Normal venous pressure	28
2 Slightly elevated venous pressure	9
3 High venous pressure	13

1 Cases with Normal Venous Pressure	28
Recovered	24
Died	4 (14%)

This chart would indicate that a large proportion of the cases showing a normal venous pressure recovered. A number of toxic cases were present in this group, indicating that a normal pressure is seen frequently in severe infection.

2 Cases with Slightly Elevated Venous Pressure	9
Recovered	8
Died	1 (11%)

The majority of patients with slight elevation of venous pressure recovered. This increase in pressure was constant throughout the illness except in one case in which the rise occurred just prior to the crisis. The normal reading was re-established at the time of crisis or towards the end of lysis in every recovered case. The fatal case, oddly, had a fall in venous pressure prior to death. Severe and mild cases were about equally divided.

3 Cases with High Venous Pressure	13
Recovered	5
Died	8 (61%)

This chart stresses the fact that the presence of a high venous pressure is associated with a high mortality. The high venous pressure was present at the time of our first observation in 8 of the cases, of which 4 recovered and 4 died. In the remaining 5 cases the venous pressure slowly increased from a normal to a high level during our observation, beginning on the third to the seventh day of the disease with one exception. In this instance a normal pressure was maintained throughout the illness, but on the day following a crisis-like reaction, the venous pressure rose

to 18 cm and death occurred the next day. Once the pressure reached a high level it remained high for the remainder of the infection with readings fluctuating from 17 cm to 22 cm, except in one instance in which there were two definite rises to 17 cm with a normal venous pressure in the interval, during eleven days of illness. The duration of high pressure varied from one day to seven days before either crisis or death. All of the fatal cases in this group had a high venous pressure at the time of death.

In the recovered cases the pressure returned to normal at the time of crisis or towards the end of lysis in four instances. The fifth case was admitted in mild cardiac failure with auricular fibrillation. The high pressure had decreased from 21 cm to 14 cm at the end of lysis and remained at a 14 cm to 16 cm level throughout convalescence, although there were no unusual cardiac symptoms.

One case developed a reinfection in the opposite lung and the venous pressure again increased to a 16 cm level and returned to normal at the second crisis. A temporary post critical rise to 17 cm after a return of venous pressure to normal at the time of crisis, was noted in one patient. The rise in pressure was not associated with evidence of reinfection and the patient made an uneventful recovery.

Venesection was performed in three instances as a measure to reduce high venous pressure. It was done virtually in a terminal stage, a time when little benefit could be expected. In the first instance, venesection of 500 cc reduced the pressure from 22 cm to 10 cm and there was marked temporary

reduction in the cyanosis, and dyspnea, and improvement in the general appearance. Three hours later the pressure had increased to 15 cm where it remained until death 6 hours after the venesection. In the second case, venesection of 400 cc. reduced the pressure from 17 cm. to 15 cm but gave no clinical improvement. Within one hour the pressure rose to 20 cm and death occurred. In the third case, venesection reduced the pressure from 20 cm to 16 cm. There was no clinical improvement. Two hours later the pressure fell to 14 cm, moisture increased in the lungs and the patient died. These few examples indicate that an attempt to reduce venous pressure late in the toxic cases offers no therapeutic benefit and may also indicate that venesection in the terminal stages of pneumonia may even be dangerous.

#### GROUP B. CASES RECEIVING INTRAVENOUS THERAPY

Early in our experience in the use of intravenous dextrose therapy in pneumonia, the solution was given in large amount and in low concentration (500 cc. of 5 to 10 per cent dextrose). During this early period no attempt was made to accurately determine the effect of a large amount of fluid on the circulation. Occasionally, however, the patients appeared clinically worse following the injections and showed evidence of circulatory embarrassment.

When we first made observations on venous pressure in cases of pneumonia, we were able to show that although many cases maintained a normal venous pressure following the administra-

tion of 500 cc of solution intravenously, in certain cases the venous pressure increased even to a critical level

of giving dextrose the blood volume is increased 19% and returns to normal within 40 minutes This temporary

## VENOUS PRESSURE RESPONSE TO INTRAVENOUS INJECTION

Example I	Time	V P	Amount of Solution
	7 25	11 cm of H <sub>2</sub> O	0
	7 30	12 cm of H <sub>2</sub> O	100 cc
	7 35	13 cm of H <sub>2</sub> O	200 cc
	7 45	14 cm of H <sub>2</sub> O	300 cc
	7 55	15 cm. of H <sub>2</sub> O	400 cc
	8 00	15 cm of H <sub>2</sub> O	450 cc
			Injection Stopped
Example II	4 30	14 cm of H <sub>2</sub> O	0
	4 50	16 cm of H <sub>2</sub> O	200 cc
	4 55	17 cm of H <sub>2</sub> O	250 cc
	5 00	18 cm of H <sub>2</sub> O	300 cc
			Injection Stopped

This type of reaction clearly indicated that under certain conditions the intravenous administration of large amounts of solution may increase the venous pressure and, by overloading the right heart, induce circulatory embarrassment in cases which otherwise might maintain a normal pressure

To avoid the danger of large amounts of fluid, the amount of solution was decreased to 200 cc of 25% dextrose Administration of fluid in this volume and percentage of dextrose frequently resulted in a temporary increase in venous pressure of 1 to 2 cm of H<sub>2</sub>O In cases with normal venous pressure there was often no increase in pressure The introduction of hypertonic dextrose solution intravenously would be expected to increase blood volume by the attraction of fluid from the tissues into the vascular channels Dr J H L Heintzelman<sup>9</sup> investigated this phase of our problem His work, which will be published separately, shows that by our method

any increase in blood volume apparently produced the temporary slight increase in venous pressure We believe that in the presence of normal or only slightly elevated venous pressure such a slight and temporary rise is of no consequence, provided the myocardial tone be adequate

The routine procedure established by our experience in the present series was as follows 200 cc of 25 per cent dextrose solution was the maximum amount of solution to be given at one time The fluid was given slowly and not more frequently than once each fourth hour Routine venous pressure readings were made daily In the presence of an elevated venous pressure more frequent readings were made. If the pressure increased above the temporary fluctuation we reduced the amount of the fluid volume injected to 100 cc, and when a persistent high venous pressure developed the procedure was discontinued Repeated small injections were frequently well tolerat-

ed, in the presence of elevated pressure. Cases admitted with an established high venous pressure received no intravenous therapy.

In the following cases intravenous injections were given from one to six times per day over a period of from 3 to 14 days

Total Number of Cases	40
1 Normal Venous Pressure	9
2 Slightly Elevated	10
3 High Venous Pressure	21
1 Cases with Normal Venous Pressure	9
Recovered	8
Died	1 (11%)

The mortality of this group is low and compares with the normal group under the usual treatment

2 Cases with Slightly Elevated Venous Pressure	10
Recovered Venous Pressure	4
Died	6 (60%)

The mortality shown by this chart is much higher than the corresponding cases in Group A. This may be explained by the fact that the cases were more toxic. As in the corresponding cases the slight elevation was present throughout the illness in the majority (8), and appeared late in the disease in the remainder (2). Also each of the recovered cases showed a return to normal pressure at the time of crisis, and all of the fatal cases had a slight elevation of pressure at death. Intensive administration of 200 cc of dextrose solution intravenously resulted in only the temporary fluctuation of 1-2 cm in venous pressure with the following exceptions. In one case the venous pressure varied from 11 cm to 15 cm during the course of disease after injections and in another there was a slight elevation just before crisis.

Both of these cases recovered. Also, in one fatal case, the administration of only 100 cc of fluid early in the infection produced a 7 cm elevation in pressure, and further intravenous medication was not attempted. In another case, on the contrary, the pressure fell slightly after each injection. This last observation is worthy of note.

3 Cases with High Venous Pressure	21
Recovered	5
Died	16 (75%)

The highest mortality is seen in this group. Clinically they represented the most toxic cases and for that reason were given intravenous therapy. A normal venous pressure at onset was seen in all of the recovered cases and eleven fatal cases. The pressure in these cases increased late in the disease, the 5th to 10th day, and each case had a high venous pressure at crisis or death. Intravenous injections were well tolerated and changes other than the temporary fluctuations were not noted early in the infection, except on two occasions. In the first, following an initial injection of 200 cc the venous pressure was raised from normal to 18 cm. It fell spontaneously illustrating a good cardiac reserve but further injection was not attempted. The second showed slight rises after each injection which quickly returned to the former level, but on two occasions rose to 18 cm. Intravenous injection was discontinued at the critical level but was resumed when a lower level was reached. Both of these cases recovered.

The general trend of development of high venous pressure and return to normal in recovery was the same in this group as in the corresponding

group under usual treatment It is our belief that with the above routine venous pressure observations the venous pressure was not unduly influenced by intravenous medication save in the exceptions noted

Venesection was performed in 9 cases of this group with the hope of reducing venous pressure so that intravenous injections of small amounts of fluid could be continued In three cases a venesection of 100 cc was done preceding an intravenous injection of the same amount In each instance the pressure was reduced slightly by venesection and returned to the previous level after intravenous This produced no demonstrable benefit In 6 cases a venesection of from 350 to 400 cc was performed preceding an intravenous injection of 75 to 100 cc Of these, three were done from the third to fifth day of disease and the venous pressure was permanently reduced from levels of 18 and 19 cm to 14 cm, and the cases recovered The remaining three cases were done virtually as terminal procedures The venous pressure was reduced from levels of 18 and 22 cm to 12 and 14 cm

respectively, and death occurred within 24 hours Repetition of venesection was done once, following a return of high pressure 24 hours after the first procedure. The pressure was again reduced but death came soon afterward

### DISCUSSION

The clinical signs of failing circulation which are so obvious in primary heart disease do not appear or are interpreted with difficulty in pneumonia, particularly in severe or toxic cases They are partially masked by the physical signs of the consolidated lung or by complications common in pneumonia Dyspnea, cyanosis, and pulmonary moisture may all be due to lung disease Palpation of an enlarged liver is often rendered impossible by abdominal distension Edema of the limbs rarely is noted

In the tabulation of total cases (table A) it will be seen that the proportion of cases showing clinical signs of circulatory failure is small compared with the proportion of cases with elevation in venous pressure Although Eyster<sup>4</sup> has stated that, "circulatory failure in an acute infection like pneu-

TABLE A

90 cases	CASES	V P	SIGNS OF CIR. FAILURE	
	37 (41%)	Normal	Cyanosis	7
			Vascular tonus changes	2
	19 (21%)	Sl Elevated	Edema of ankles	2
			(1 with old cardiac disease)	
			Cyanosis	6
	34 (37.7%)	High	Cyanosis	All
			Positive centrifugal venous pulse	1
			Vasomotor changes	2
			Icterus	3
			Enlarged liver	2
			Edema	1
			Valve disease, Plus edema	1

monia does not appear to differ in any essential details from the same condition developing in primary heart disease," the infrequent appearance of the cardinal signs in pneumonia may be due to the relatively short duration of circulatory embarrassment. This is especially significant in that two of the four cases with edema were cases with old organic heart disease. If venous pressure is of value in estimating the circulatory state in primary heart disease it appears to be of an even greater clinical use in pneumonia where the usual pathognomonic signs are of so little value.

Blood pressure and pulse rate have been used as guides of severity of pneumonic cases and these criteria have been used as prognostic signs. It has been declared by various writers that a low or decreasing blood pressure is evidence of failing circulation in pneumonia. It is known that whereas venous pressure bears a direct relationship to cardiac efficiency, it bears no constant relationship to blood pressure. Blood pressure records were made on 70 cases. Table B illustrates the number of cases of high, average, and low blood pressure occurring in the presence of normal, slightly elevated, and high venous pressure. It will

be seen that 71.4 per cent of the cases had an average blood pressure, 11.4 per cent had high and 17.1 per cent had low blood pressure.

It is interesting that the majority of cases with low blood pressure occurred with a normal venous pressure, and the great majority recovered. The highest mortality comes in the average blood pressure group with increased venous pressure. A high blood pressure appears to have a greater mortality significance than low pressure in this small series.

The pulse rate has been, in our experience, a valuable index of severity or toxicity in pneumonia. An elevation in rate to 120 per minute or greater was considered evidence of severity. We were thus particularly interested to check venous pressure records with the pulse rate. Table C presents this data for the 90 cases.

It will be seen that in the group with normal venous pressure the majority of cases had low pulse rates, in the slightly elevated group the proportion is about equal, while in the high venous pressure group the majority have a high pulse rate. The general mortality for cases with high pulse rate is 63.6% and low pulse rate 19.1%, for a practically equal num-

TABLE B

VENOUS PRESSURE	BLOOD PRESSURE					
	HIGH		AVERAGE		LOW	
	Lived	Died	Lived	Died	Lived	Died
Normal	3	1	19	2	7	1
Slightly Elevated	1	1	5	4	2	0
High	1	1	5	15	1	1
	—	—	—	—	—	—
Total	5	3	29	21	10	2
	Mort 37.5%		Mort 42%		Mort 16.6%	

TABLE C

VENOUS PRESSURE	PULSE RATE					
	Above 120			Below 120		
	Lived	Died	Mort	Lived	Died	Mort
Normal	9	2	18%	23	3	11.5%
Slightly Elevated	3	5	62.5%	9	2	18%
High	4	21	87.5%	6	4	40%

ber of cases. From the data presented previously there is also a definite correlation between degree of venous pressure and mortality. The mortality in normal venous pressure cases is 13.5%, in slightly elevated pressure 36%, and in high pressure 70%. Comparing these mortality figures with the pulse rate mortality figures it will be seen that in each venous pressure group the mortality in cases with pulse rate above 120 is greater than in cases below 120. The lowest mortality occurs with normal venous pressure and slow pulse rate, the highest mortality with high venous pressure and rapid pulse rate.

From our experience we believe that a rising venous pressure is the earliest method of recognizing circulatory failure in pneumonia. Used in conjunction with other clinical phases of the disease we feel that these observations have been to us of considerable bedside value.

Venous pressure observations form a basis for measuring the circulatory condition of the patient at the time the reading is made. A single reading is of relatively little value. Repeated readings offer a graphic record of the trend of circulatory state. They are not a means of predicting the outcome of the case for the outcome depends on the ability of the heart to withstand

the added work. For example, a case running a normal course may suddenly develop failure, and on the contrary, a case with a persistently high venous pressure may recover if sufficient reserve is maintained. However, venous hypertension has some prognostic value, in that, we know such changes are associated with a high mortality. A progressively rising venous pressure, particularly late in the infection, is most significant of a bad prognosis.

Sudden fluctuations are not uncommon but in general the development of a high venous pressure extends over a period of a few days. The three cases developing sudden increase of venous pressure after crisis seem of particular significance. The mechanism of such a reaction is difficult to explain but it points out that sudden changes after crisis may be due to acute circulatory failure which may be fatal.

We do not disregard the fact that death in pneumonia is also induced by causes other than circulatory failure. This is shown by fatal cases which have maintained a normal venous pressure throughout the disease. Because of the high incidence of circulatory failure in pneumonia and its definite relationship to mortality, every patient during treatment must be considered a potential case of circulatory failure.



The method of intravenous hypertonic dextrose treatment used in this series, we believe, added no additional risk to the circulatory apparatus when guided by venous pressure records

The use of venesection in toxic and infectious states involves different problems than in primary heart disease, where a purely mechanical problem is at hand. Relief of early high venous pressure by venesection may be of benefit, as shown by three cases. At this period mechanical relief by venesection may allow a heart with good reserve to gain a permanent advantage. As disease progresses, the effect of toxemia and anemia decreases a possible therapeutic value and late in the disease venesection may even be dangerous.

#### CONCLUSIONS

1 Observations on the estimation of venous pressure by the indirect method (Eyster and Hooker) have been made on a series of cases of pneumonia

2 An increase of venous pressure is evidence of circulatory failure in pneumonia

3 The estimation of venous pressure is of particular value in recognizing circulatory failure in pneumonia, because the usual signs of congestive heart failure are difficult to recognize in this disease

4 The correlation of venous pressure and pulse rate offers the best means of estimating circulatory failure in pneumonia

5 The presence of increased venous pressure is associated with an increased mortality in pneumonia

6 Venous pressure estimations are of value in controlling intravenous therapy in pneumonia

7 Venesection is controlled by venous pressure determinations, and under certain early conditions may be of value, but in general, late in the pneumonic infection is of little therapeutic worth

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# Acute Coronary Occlusion

## A Clinical and Electrocardiographic Study of Twenty Cases

By LOUIS H. SIGLER, M.D., *Brooklyn, N. Y.*

ALTHOUGH the pathologic changes associating embolic, thrombotic and endarteritic occlusion of the coronary arteries have been fully described for many years, the clinical picture resulting from such changes seems to have come into prominence only recently. As late as 1906, Broadbent stated that "there are no characteristic physical signs or symptoms by which thrombosis of the coronary arteries can be diagnosed." Blumer, in the 1915 Edition of Osler and McCrae's "Modern Medicine" stated that the symptoms of this condition are "not very characteristic and it is only rarely that the lesion can be diagnosed during life." The diagnosis of coronary artery thrombosis or embolism is at best a question of probabilities. The same view was held by Price in 1918 who stated that "complete and abrupt closure of a coronary artery is usually fatal. If the vessel is small the patient may recover, but the condition is one which is recognized with difficulty during life."

These views have changed in recent years. Due to a greater prevalence of arteriosclerotic heart disease and to the refinement in the differential diagnosis of the various forms of such dis-

ease, we came to recognize a definite clinical syndrome, pathognomonic of coronary occlusion. Concomitant with the clinical syndrome, certain pathognomonic electrocardiographic changes have been observed and have come to be considered characteristic of the disease. Furthermore, we now realize that the disease is usually not immediately fatal, and including the milder forms of occlusion, is rather prevalent and has a favorable prognosis.

Although the clinical syndrome has been repeatedly described, the association of its various manifestations with the anatomico-physiologic changes taking place in the heart have not been stressed. This paper is an attempt to do so, and to bring out certain important factors in the electrocardiographic study of such cases. The paper is based on a study of twenty cases in various phases of the disease.

### CASE REPORTS

*Case I.* A S., female, housewife, 58 years old, was suffering from a mild form of diabetes and hypertension for fifteen years. While at perfect rest she was suddenly seized, one day, with excruciating pain in the substernal region radiating to the left shoulder, together with vomiting, dizziness and a sensation of impending dissolution. I saw her eighteen hours after the onset of symp-

toms at which time I found her to be markedly dyspneic, her color was ashen, and a cold perspiration covered her body. Her lungs showed numerous râles at the bases posteriorly. The heart was enlarged to the left and right, sounds were almost inaudible, rate was about 120, rhythm regular. The blood pressure was systolic 100, diastolic 80. The liver was enlarged and tender.

The next few days she seemed to be heading towards recovery. The pain subsided. The temperature came down from 101 F on the second day to normal on the fourth day. Eight days after the onset, however, she suddenly developed severe pain in the left lower chest together with dyspnea, cough and bloody expectoration. There was evidence of infarction of the lower lobe of the left lung the following day, with signs of onset of pulmonary edema. She died three days later.

The electrocardiographic tracing (Fig 1) taken ten days after the onset, showed a simple tachycardia with delayed P-R conduction time, about 23 second, and a low S-T take-off in Leads 1 and 2. There was a tendency towards left axis deviation.

*Case II* M E, female, 66 years old, domestic help, was suddenly seized, about one-half hour after breakfast, with severe epigastric pain, vomiting and collapse. The condition was relieved after three hours by morphine. The next day, her temperature was 100 F, pulse 110, very irregular, and respirations 25. The leucocyte count was 14,200. The heart sounds were muffled, and a definite gallop rhythm was present. There was marked peripheral arteriosclerosis.

The electrocardiogram, four days after the onset (Fig 2), showed a marked sinus arrhythmia, left axis deviation, slurring of the S wave in the first lead and notching of QRS in the third lead, depression of the S-T segment in first lead, and elevation and rounding of the R-T segment in the second and third leads, with markedly negative T waves in those leads. About two weeks later (Fig 3), the S-T segment in the first lead was on the isoelectric level, while the T waves in the second and third leads were more markedly negative. The S wave in the

first lead and the R wave in the third lead were of much smaller amplitude.

Three weeks after the onset she felt quite well and insisted upon resuming her work. I am informed that she is living and feels quite well at present, two years after the attack.

*Case III* J K, male, 77 years old, retired merchant, with a negative past history, was suddenly seized with excruciating pain in the region of both breasts, radiating to the left arm, left leg and to the back. It lasted several hours and was only partially relieved by morphine. He had had a similar but milder attack three months before, lasting ten minutes, which was considered to be a form of indigestion, as it was relieved by belching. I saw him twenty hours after the onset of the second attack at which time he was ashen in appearance, respirations were rapid, and his body was covered with a cold, clammy perspiration. He had marked peripheral arteriosclerosis. The heart was of normal size, sounds hardly audible, with a total irregularity, the ventricular rate being 120 and pulse rate 90. The pulse could hardly be felt. The liver extended about four inches below the costal margin, and was tender.

The next day he showed definite signs of pulmonary infarction. His temperature was 101 F, ventricular rate about 139 and pulse rate 104. The electrocardiogram (Fig 4) showed auricular fibrillation and slurring of the QRS complexes in all leads. The T wave changes were not distinctly discernible, due to the fibrillation, but they seemed to be negative.

His subsequent course was rapidly downward. He had three more attacks of precordial pain during the following three months, and died about four months after the onset.

*Case IV* B M, female, 55 years old, with a history of hypertension of several years standing, and occasional precordial pain coming on after exertion for the past year, suddenly developed excruciating retrosternal pain, radiating to the throat, and associated with a sense of strangulation. The pain appeared while the patient was at per-

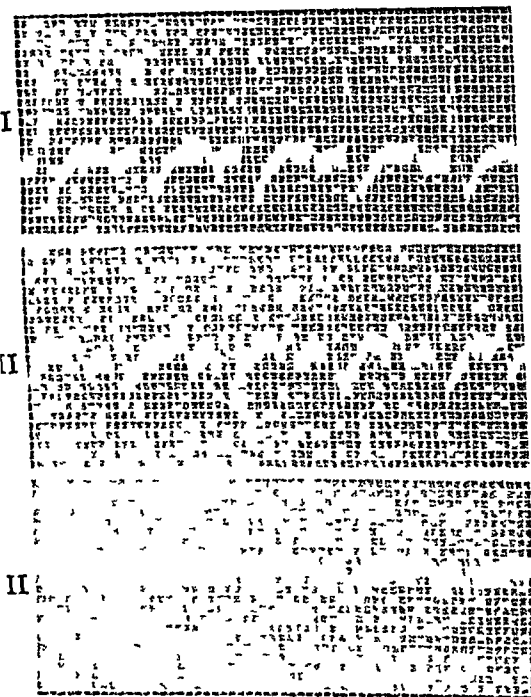


FIG 1

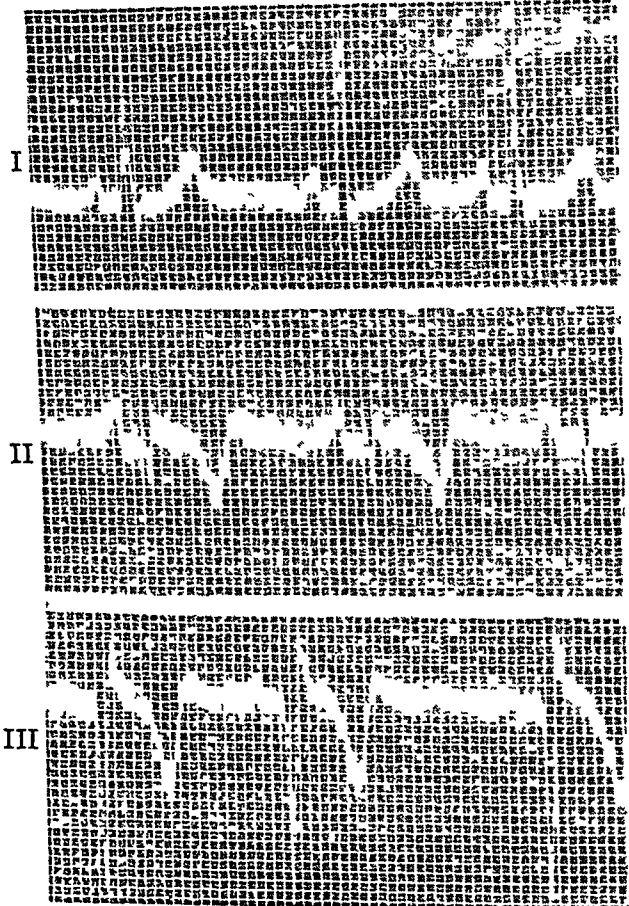


FIG 3

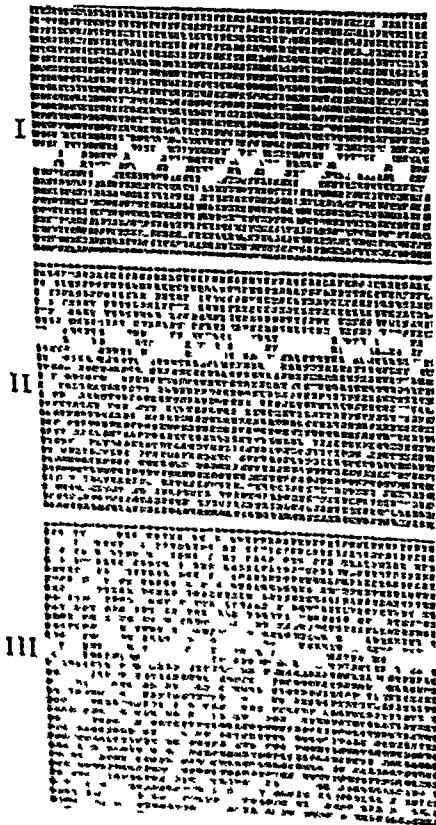


FIG 2

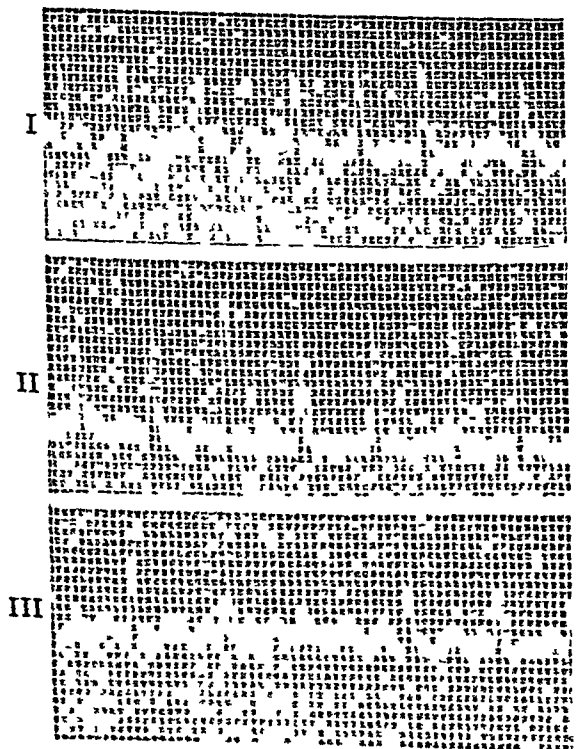


FIG 4

fect rest, after a mid-day meal, and lasted two hours

I saw her one week after the onset, when she showed slight cyanosis, and marked dyspnea. Her heart was enlarged to the left, sounds distant, almost inaudible, rate 105, rhythm regular. There was moderate peripheral arteriosclerosis. The blood pressure was systolic 150 and diastolic 115.

The electrocardiogram (Fig 5) showed left axis deviation, slurring of the S and R waves in the first and third leads and notching of the S wave in the second lead, delayed QRS conduction time to 12 of a second, the S-T and R-T segments in all leads were above the isoelectric line, and there was a negative T wave in the third lead.

She is still alive, 15 months after the attack.

*Case V* R K, female, 61 year old, with a history of hypertension of ten years standing, was suddenly seized with excruciating midsternal pressure and pain, radiating to the left arm, associated with a sensation of fainting, coldness of the whole body, and marked sweating. The pain lasted about ten hours. I saw her at the end of four weeks, when she appeared pale and markedly irritable. Her heart was enlarged to the left, and sounds were muffled. The lungs showed numerous basal râles. The blood pressure was systolic 150, diastolic 110.

The electrocardiogram (Fig 6), showed left axis deviation, rounding of the S-T segment in the second lead, high R-T take-off in the third lead, markedly negative T wave in the second and third leads, especially in the latter, and increase in the height of the T wave in the first lead.

I saw her four months later at which time her heart sounds were found to be markedly improved, and her blood pressure was systolic 210 and diastolic 130. An electrocardiogram taken at this time (Fig 7), did not show any definite left axis deviation, and the T wave in the second and third leads was less negative. Eight months later, the electrocardiogram (Fig 8) showed a negative T wave only in the third lead. Physically she was found to be greatly im-

proved, but was subject to repeated precordial pain.

*Case VI* A C, male, 38 years old, dentist, never had any symptoms of heart disease. He smoked considerably all his life and was subject to attacks of angioneurotic edema. While sitting at rest one day, he suddenly felt a very severe "tightening" in the center of the sternum which lasted fifteen minutes and subsided, leaving him with no other ill effects than an apprehension of its return. Two days later, he got a second and far more severe attack lasting several hours and requiring large doses of morphine to give partial relief. This attack was associated with a sensation of fainting and a feeling of imminent death. His whole body was covered with a cold perspiration. The following day he felt quite comfortable. I saw him at my office three days after the second attack when his heart was of normal size and shape, sounds of fair quality, rate 72, rhythm regular. The peripheral vessels were slightly thickened. The electrocardiogram (Fig 9) showed left axis deviation, rounding and slight elevation of the R-T segment in the first lead, slightly negative T wave in the second lead and markedly negative T wave in the third lead.

I saw him again ten weeks later and found his condition to be the same as before. Aside from a dull precordial ache, he had no complaints. The electrocardiogram (Fig 10) then showed a definitely negative T wave in the second and third leads with slight depression of the R-T segments in those leads.

*Case VII* J T, male, 51 years old, with a history of hypertension for several years was suddenly seized, after his evening meal, with a severe sense of "tightness" in the precordium and epigastrium, radiating to both arms. This was associated with collapse and cold perspiration. Large doses of morphine gave relief after three hours. I saw him about four hours after the onset when he appeared to be quite comfortable. He was markedly obese and slightly cyanotic. His heart was enlarged to the left, sounds were of poor quality and rhythm regular. The blood pressure was systolic 120 and dia-

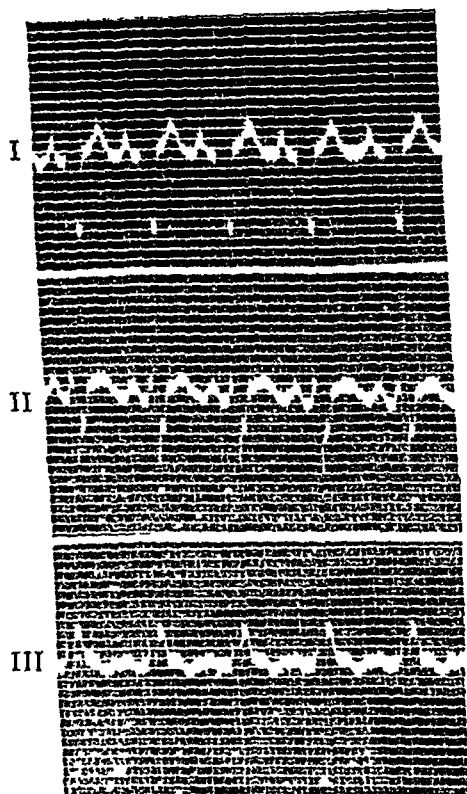


FIG 5

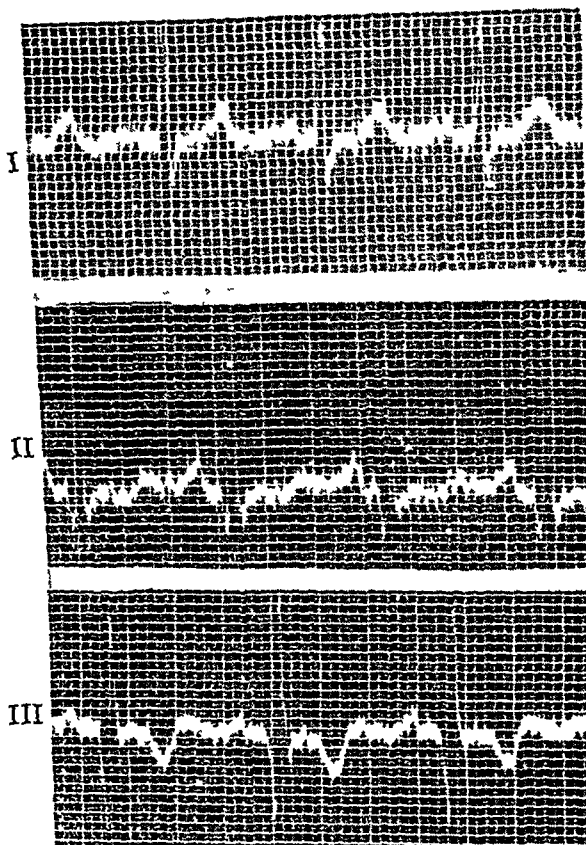


FIG 7

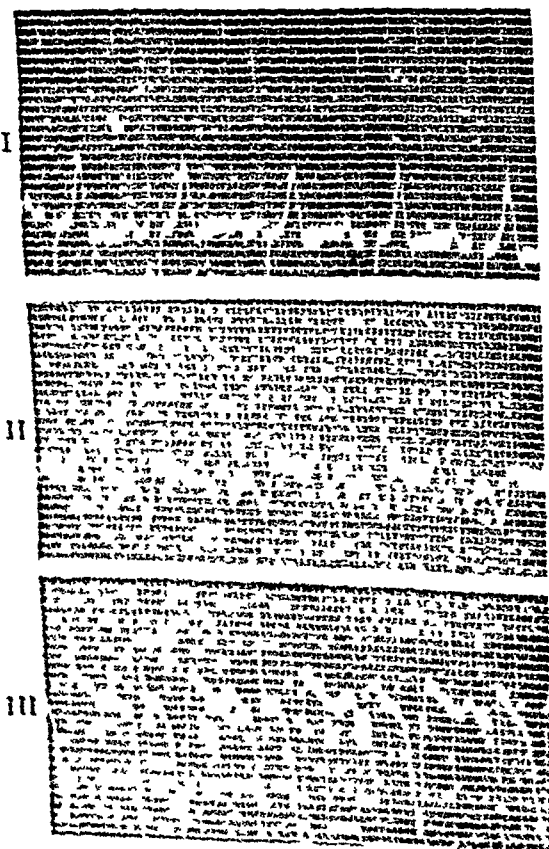


FIG 6

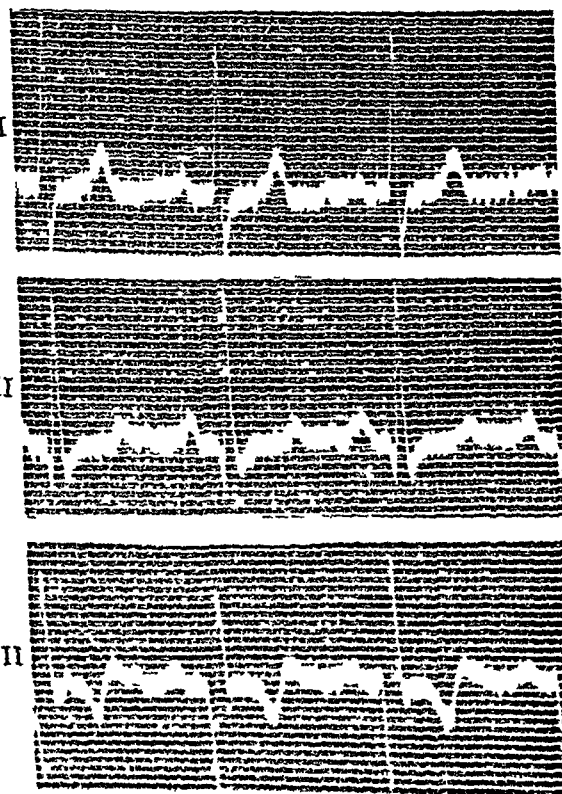


FIG 8

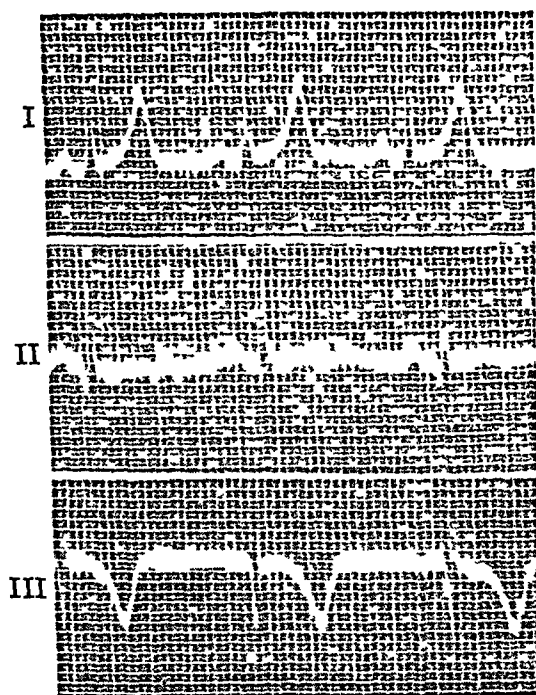


FIG 9

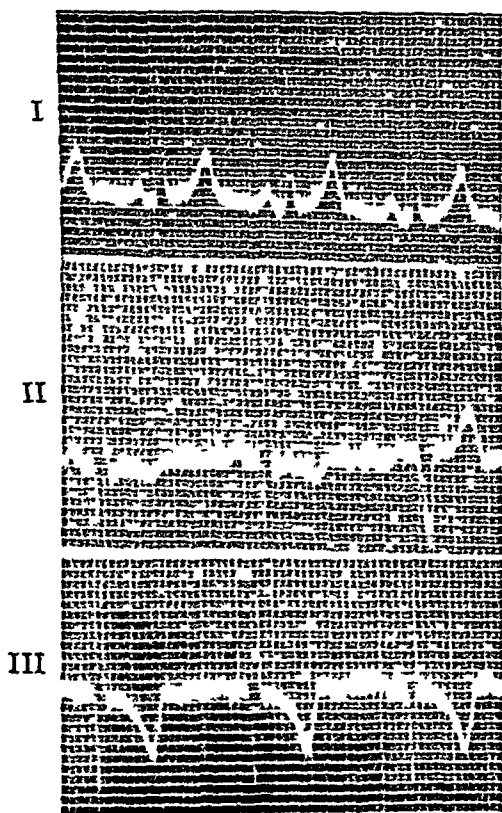


FIG 10

stolic 80 The lungs showed numerous basal râles The peripheral vessels were markedly sclerotic The next day his temperature was 101 F, pulse 72, and blood pressure was systolic 110, diastolic 80

The electrocardiogram (Fig 11) showed left axis deviation, notching of the R wave in the second lead, rounding and elevation of the R-T segment, with a markedly negative T wave in the second and third leads

At present, 10 months after the attack, he feels well and does considerable work with comfort

*Case VIII—M T*, male, 50 years old, laborer, was always a hard worker and had never had any symptoms indicative of heart disease Aside from a severe attack of influenza eight years ago, and considerable use of tobacco, his history is essentially negative

While working, one morning, he was suddenly seized with severe precordial pain and oppression lasting four hours No untoward effects apparently followed this attack, as he resumed his work two days later without discomfort Six months later, he had a more severe attack of a similar nature, associated with collapse Three-fourths grain of morphine were necessary to give relief This attack lasted 24 hours Since then he has experienced shortness of breath and dull precordial pain on any moderate exertion

I saw him three weeks after the second attack when he presented a normal sized heart The first sound was muffled and split The peripheral vessels were markedly sclerotic, pulse weak, and blood pressure was systolic 120, diastolic 95 The electrocardiogram (Fig 12) showed rounding of the R-T segment and a markedly negative T wave in the second and third leads

*Case IX—M H*, male, 62 years old, merchant was suddenly seized with excruciating pain in the epigastrium, radiating behind the sternum to the left shoulder, together with belching, cold perspiration, vomiting and a sense of suffocation He was partially relieved by morphine after several hours This was followed for many weeks by dull precordial pain, palpitation, marked mental depression, dyspnea and great weakness There was a rise in temperature for two weeks



following the onset, ranging between 100 and 101½ F

Examination one week after the onset, showed his heart to be of normal size, the first sound muffled, and an occasional pericardial friction rub was audible at the apex. The pulse was very weak, and the blood pressure was systolic 100 and diastolic 70. These findings were practically the same throughout the course of his illness, lasting about four months, except that the pericardial friction rub disappeared after two days, and a presystolic gallop rhythm appeared two months later. He died suddenly, while sitting up in a chair.

Four electrocardiograms in his case are reproduced. The first one (Fig 13) was done about one month after the onset and showed left axis deviation, isoelectric T wave in the second lead, rounding of the S-T segment and negative T wave in the third lead. Five weeks later (Fig 14), the left axis deviation was not marked, and the second and third leads showed a negative T wave. Four weeks later the tracing (Fig 15) showed absence of left axis deviation. Still later the electrocardiogram (Fig 16) showed a tendency towards right axis deviation, and the T wave in the second and third leads was not so deep.

*Case X—W B C*, male, 58 years old, bank guard, was a heavy smoker all his life, had pleuro-pneumonia at 29 years of age, was subject to frequent colds, and had hypertension for several years. Coming home from work one day, he was suddenly seized with severe pain in the epigastrium radiating to the retrosternal region and to the back, with fainting and cold perspiration. The pain lasted four hours and was relieved by morphine. Since then he was subject to exertion dyspnea and dull precordial pain.

I saw him eight months after the attack when he presented marked obesity and considerable peripheral arteriosclerosis. His face had a slight cyanotic flush. His tonsils were hypertrophied and diseased. The lungs were emphysematous and numerous inspiratory rales were heard over the bases. The heart was markedly enlarged, first sound weak, rate 90, rhythm regular. The blood pressure was systolic 158, diastolic 100.

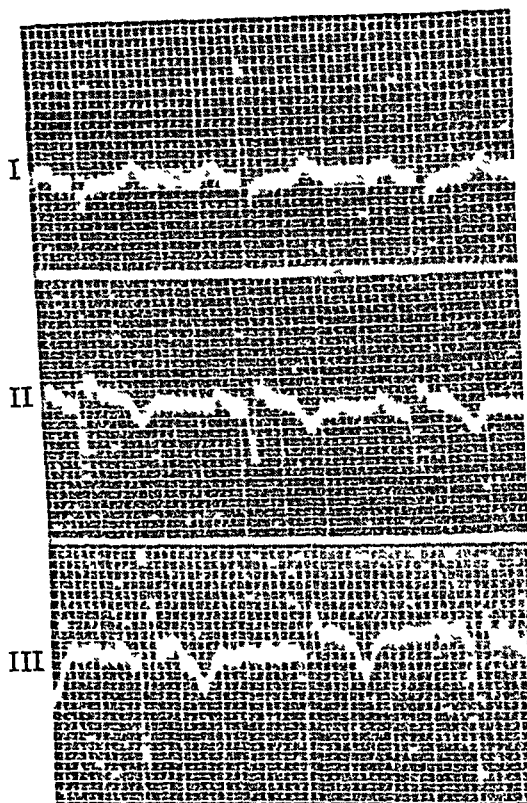


FIG 11

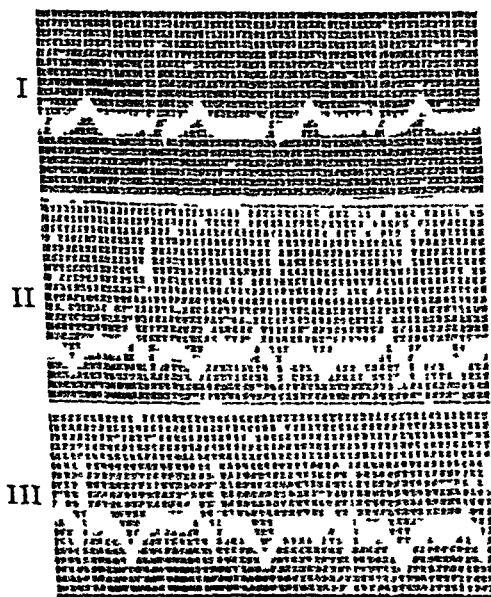


FIG 12



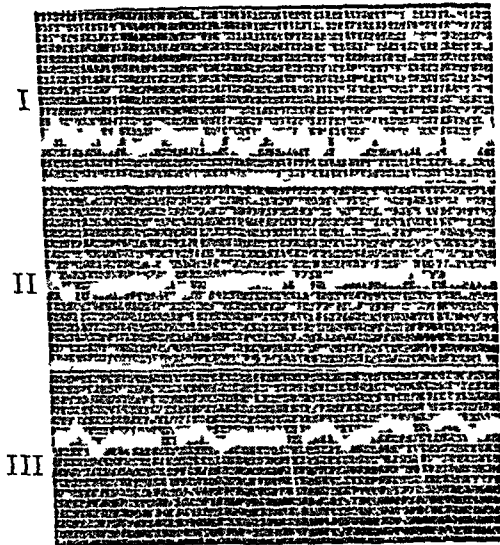


FIG 13

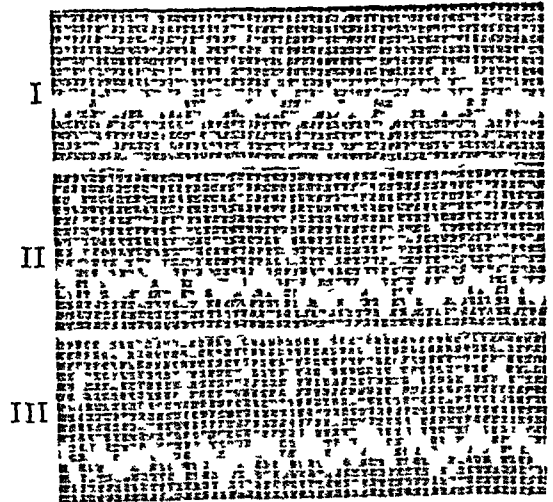


FIG 15

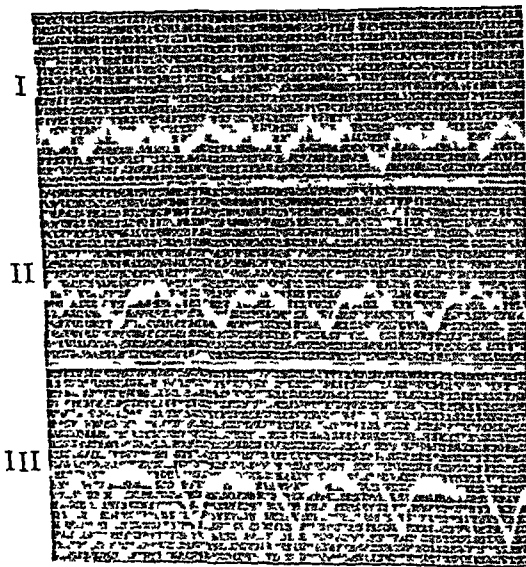


FIG 14

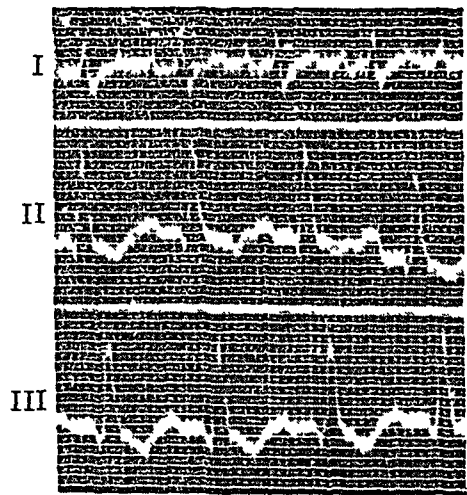


FIG 16

The electrocardiogram (Fig 17) showed left axis deviation, slurring of the S wave in the third lead, disphasic T wave in the first and second leads and isoelectric T wave in the third lead

*Case XI*—B Z, male, 53 years old, painter, with an essentially negative past history. He was always a hard worker, a heavy user of tobacco, and of a rather irritable nervous disposition. While at perfect rest one day after his evening meal, he suddenly felt a severe oppression in the epigastrium and precordium, radiating to the neck, together

with a cold sweat, vomiting and a sensation of fainting. This subsided in four hours, after the administration of morphine. The following two days he was running a temperature of about 101 F, had marked tenderness over the epigastrium, pulse was very weak and heart sounds poor. His family physician considered his case one of acute cholecystitis. Since that attack, the patient has experienced dyspnea on moderate exertion.

I examined him about five months after the onset, at which time he presented a

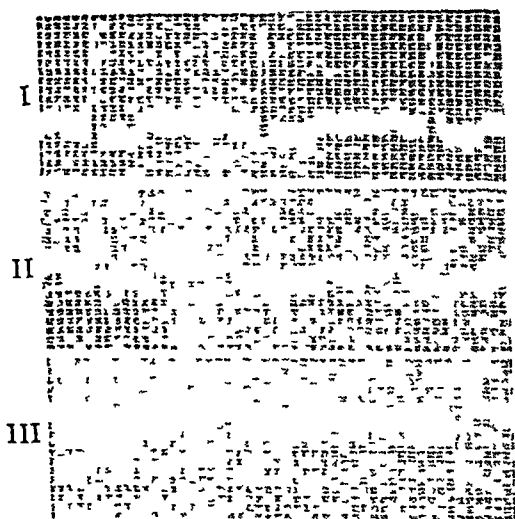


FIG 17

marked facial pallor. The peripheral vessels were markedly sclerotic. His blood pressure was systolic 150, diastolic 90. The lungs showed a few moist basal râles. The heart was of normal size and shape, rate 65, regular rhythm. The first sound was weak, and was partly replaced by a harsh systolic murmur which was transmitted to the axilla and midsternum.

The electrocardiogram (Fig 18) showed left axis deviation, slurring and notching of the QRS complex in the second and third leads, and negative T wave in all leads.

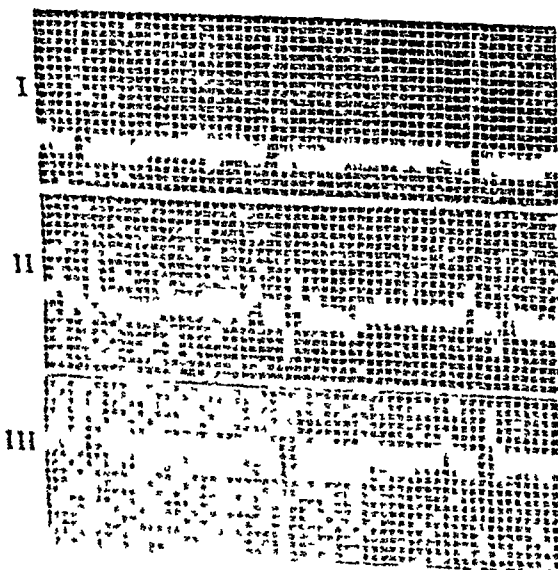


FIG 18

**Case XII—M L**, male, 52 years old, tailor, was suddenly seized at work with a severe attack of "heartburn," together with a cold perspiration and a sensation of fainting. It subsided in 20 minutes with apparently no ill effects. Another similar short attack recurred four weeks later. Five weeks after the second attack, while at work, he suddenly felt an excruciating burning in the epigastrium radiating behind the sternum to the neck, as if "hot smoke was rolling up from the stomach to the neck." He fainted and when revived, his whole body was covered with a cold sweat.

Examination revealed an individual in extreme anguish. He was gasping for air, and complained of an extreme discomfort and pressure in the epigastrium radiating to the neck and to the left shoulder. He was very restless, tossed around from side to side, and felt as if he was choking. His color was ashen, pulse almost imperceptible, rate about 110, regular. The heart was markedly enlarged to the right, the first sound was muffled and almost inaudible. The right lung showed almost complete suppression of breath sounds, and numerous moist râles were heard at the bases. The liver extended about four inches below the costal margin. The blood pressure was systolic 80, diastolic 70.

An electrocardiogram (Fig 19) done at that time showed very low voltage curves,

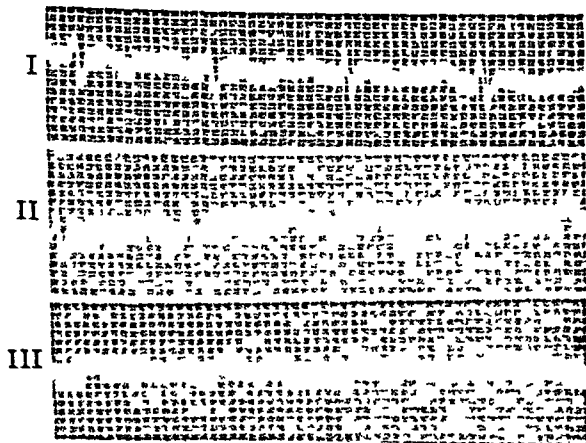


FIG 19

slurring of the QRS complex in all leads, and rounding of the S-T segment with negative T wave in the first lead

Three days later there was a definite pericardial friction rub in the lower sternal region over an area  $2\frac{1}{2}$  inches wide between the levels of the third and fifth ribs. He showed progressive improvement within the next two weeks. At the present writing, about three months after the last attack, he feels quite well. The heart sounds are of good quality with the exception of a slight muffling of the first sound. The blood pressure is systolic 132, diastolic 88. The liver is normal and the lungs are negative.

The electrocardiogram (Fig 20) shows higher complexes, and the T wave in lead I is isoelectric.

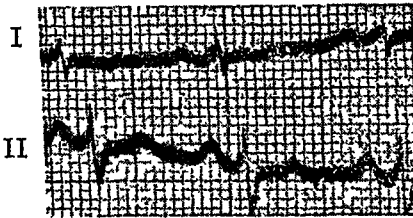


FIG 20

*Case XIII*—M A M, male, 52 years old, complained of continuous dull precordial ache and occasional epigastric pain on walking. His father died suddenly at 47 and mother at 50 of causes unknown to the patient. He was always a heavy tobacco smoker.

The present complaint dates back nine months, when taking a cold shower, he suddenly experienced a very sharp pain in the precordium, which subsided on the application of heat. Five days later, he again felt a most excruciating pain in the precordium lasting six hours. The pain came while at rest and was accompanied by great shock. He was confined to bed six weeks.

Examination nine months after that attack showed the heart to be greatly enlarged to the left and also slightly to the right. The first sound was slightly muffled. The lungs showed an occasional moist r  le at the bases. The peripheral vessels were slightly thickened and the blood pressure was systolic 140, and diastolic 90.

The electrocardiogram (Fig 21) showed left axis deviation, slight depression of the R-T segment in the third lead, with a definitely negative T wave in the second and third leads.

*Case XIV*—S O, male, 53 years old, plasterer, who was always healthy, suddenly developed severe palpitation with marked precordial oppression and weakness, compelling him to stay in bed a week. One year later he suddenly experienced another attack of severe palpitation and a most annoying pain in the left precordium, radiating to the back. He felt like vomiting and a cold perspiration covered his body. The attack lasted two hours and gradually subsided. Since then he had milder recurring attacks and he noticed that he became very short of breath on the slightest exertion.

Four days after the last severe attack he showed an ashen-brownish color, but he appeared to be rather comfortable. The heart was of normal size and shape, first sound short and split, rate about 58, rhythm regular. The peripheral vessels were markedly sclerotic, and the blood pressure was systolic 120, diastolic 80. An occasional moist r  le was heard at the bases of the lungs.

The electrocardiogram (Fig 22) showed left axis deviation, negative T wave in the first lead, elevation of the S-T segment and abnormally high T waves in the second and third leads.

Seven weeks later the patient felt greatly improved. The heart sounds were of good quality, rate 64, rhythm regular. The electrocardiogram (Fig 23) still showed left axis deviation, QRS of lower voltage, T wave in the first lead positive, while in the second and third leads, of much lower amplitude.

*Case XV*—J J Mc, male, 63 years old, heavy tobacco smoker, but whose history is otherwise negative, suddenly experienced a severe precordial tightening while walking. It lasted ten minutes and stopped spontaneously. Towards the middle of the night, he was awakened by a severe, lancinating precordial pain, radiating to both arms, accompanied by cold perspiration and a sensation of impending dissolution. The attack lasted seven hours and was only partially relieved.

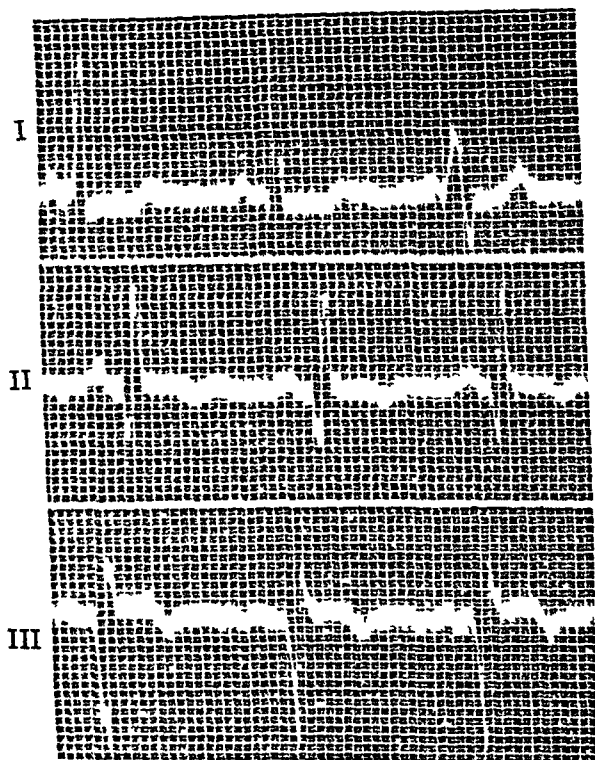


FIG 21

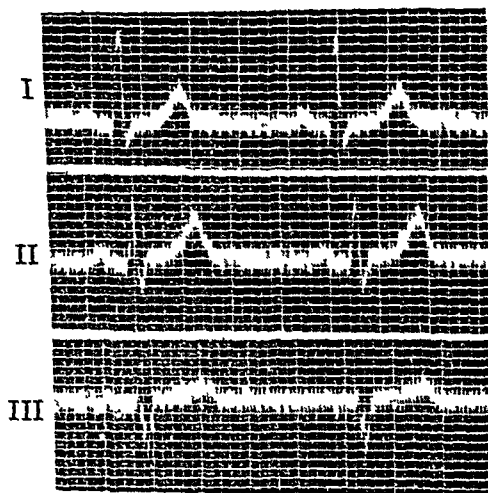


FIG 23

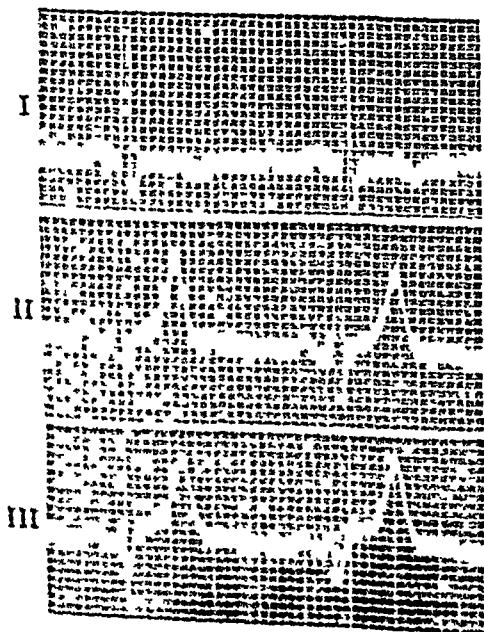


FIG 22

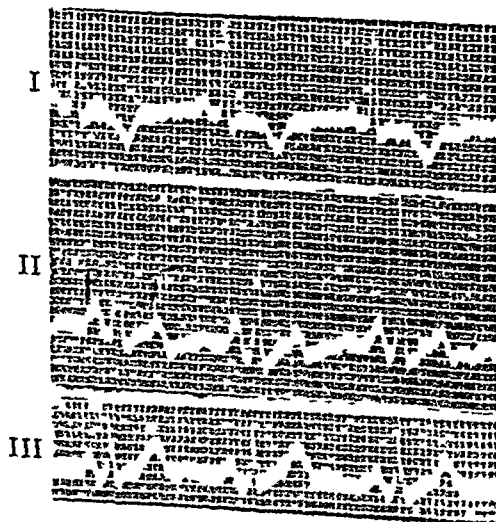


FIG 24

by morphine. Since then he is experiencing some precordial pain on exertion, radiating to the upper abdomen

Examination three months after the onset showed a very pale, elderly male with marked peripheral arteriosclerosis. His heart was of the longitudinal type, but no definite enlargement could be made out. The first sound was muffled, rate was 70, rhythm regular. The blood pressure was systolic 160, diastolic 80.

The electrocardiogram (Fig 24) showed a rounding out and slight depression of the S-T segment and negative T wave in the first lead.

**Case XVI**—A S, male, 60 years old, tailor with a history of precordial pain and oppression on exertion for the past seven years, was suddenly awakened one night with excruciating pain in the upper sternal region radiating to both arms and the back, between the scapulae. The pain lasted three hours, and required considerable morphine for relief. Since then he experienced precordial "tightness" and pain on the slightest effort.

Examination four weeks after the attack showed the heart to be slightly enlarged to the left, rate 88, rhythm regular. There was accentuation and slight splitting of the first sound. The peripheral vessels were markedly sclerotic and the blood pressure was systolic 120, diastolic 90. He was dyspneic and his color was ashen.

The electrocardiogram (Fig 25) showed left axis deviation, depression of the S-T and R-T segment in the first and second leads, and diphasic T wave in those leads.

**Case XVII**—M S, male, 74 years old, merchant, was suddenly seized two hours after an evening meal, with severe epigastric pain, radiating to the retrosternal region, associated with marked belching and cold sweat. The attack lasted eight hours. The following three days he was running a temperature of 100 to 101½ F, heart was regular, sounds of poor quality, rate 100.

I saw him two weeks after the attack when he revealed nothing abnormal except for muffling of the first heart sound, and a few moist râles at the bases of both lungs. The

electrocardiogram (Fig 26) showed left axis deviation, slight rounding of the S-T segment, negative T wave in the first lead, and splintering of the QRS complex in the third lead.

**Case XVIII**—J V L, male, 60 years old, clerk, complained of palpitation, epigastric heaviness, pain in the apical region of the heart and weakness, following any exertion or coming on after a meal. He was always a heavy cigarette smoker, and was told four years ago that he had hypertension.

The present complaints followed an attack of "acute indigestion" two years ago, characterized by sudden epigastric pain with heaviness, belching, and extreme palpitation, as if someone was "bouncing" him over his heart. His entire body was "drenched." The condition lasted eight hours.

Examination, two years after that incident, showed an obese individual, slight exophthalmos, teeth infected, tonsils enlarged and diseased. The bases of the lungs showed an occasional moist râle. The heart was greatly enlarged to the left, and the aortic arch was markedly widened. The first sound was

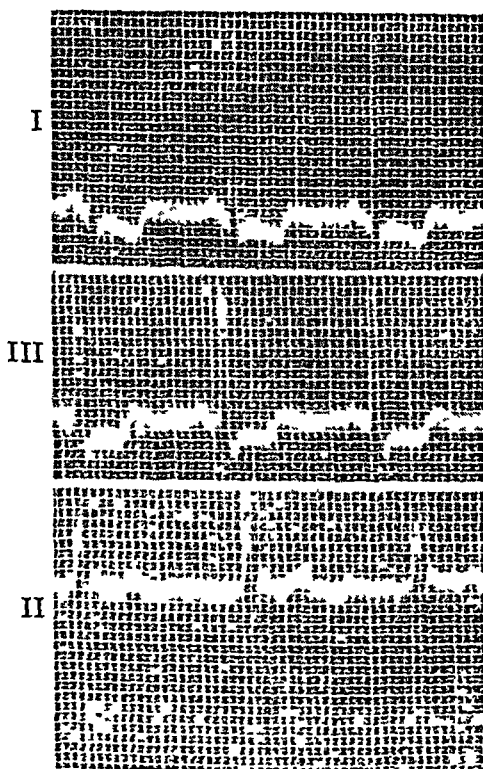


FIG 25

long, muffled and split and a rough systolic murmur was heard over the aortic area, transmitted to the apex. The peripheral vessels were markedly sclerotic, and the blood pressure was systolic 160, diastolic 100.

The electrocardiogram (Fig 27) showed left axis deviation, slurring of the QRS complex in all leads, rounding of the S-T segment and negative T wave in the first and second leads.

*Case XIX*—A W, male, 62 years old, waiter, gave a history of chancre 22 years

ago for which he was treated with salvarsan. For the past few years he was subject to a productive cough, slight headache, occasional dizziness and slight shortness of breath on exertion.

On the day of examination he suddenly experienced a burning sensation in his throat and epigastrium with a sharp pain in the left shoulder. He became markedly prostrated and collapsed.

Examination revealed an elderly male in marked agony. His skin and mucous membrane were pale, pupils were contracted and

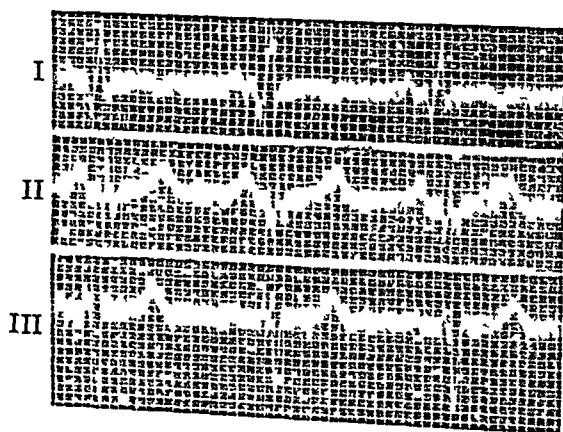


FIG 26

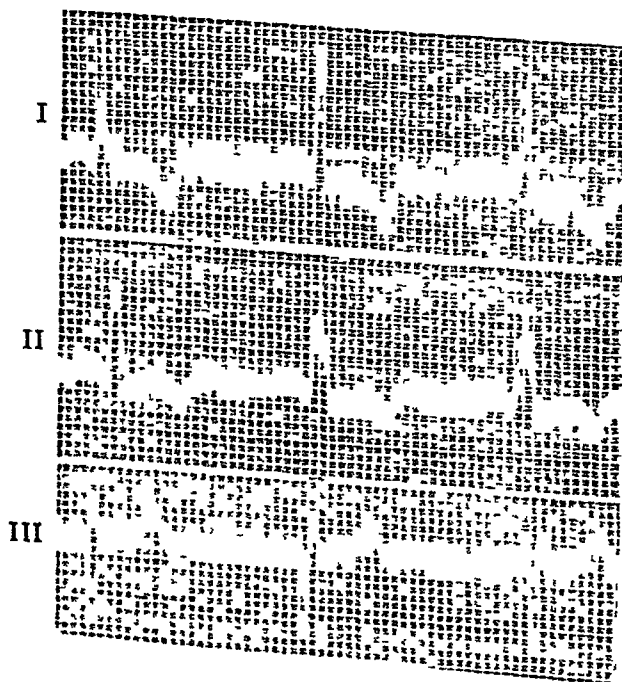


FIG 27

reacted sluggishly to light. The peripheral vessels were markedly sclerotic, the finger tips cyanotic and clubbed. Respirations were labored. The heart was of normal size, regular rhythm rate about 40, sounds almost inaudible. The lungs showed emphysematous breathing and numerous râles were heard. The abdominal wall was markedly rigid, especially the right rectus muscle. The white cell count on the second day was 11,800, with a differential of 80% polymorphonuclear leucocytes. The blood chemistry showed urea nitrogen 30, creatinin 2.5, uric acid 6.5 and glucose 120 milligrams per 100 c.c. The blood Wasserman was negative. The urine showed considerable albumin, many hyaline and coarsely granular casts.

The electrocardiogram, done on the second day (Fig. 28), showed marked sinus bradycardia, low voltage QRS wave, left axis deviation, isoelectric T wave with tendency towards being negative, in the first lead, and high R-T takeoff in the second and third leads.

He subsequently showed progressive improvement. His temperature ranged between 97 and 99 and the pulse rose to 70 and became more full.

I saw him again on May 2nd, 1930, at which time he felt well, and was working for three weeks as waiter, without any discomfort. The heart sounds were of fair quality. The electrocardiogram at that time (Fig. 29), still showed low voltage curves, but there was no left axis deviation. The T wave in the first lead was definitely negative, and the R-T interval in the second and third leads returned to the iso-electric line. There were occasional premature contractions originating in the right ventricle.

*Case XX*—I. M., male, 60 years old, tailor, hypertensive of several years standing, and subject to occasional precordial pain for the past five years, appearing on exertion. A year ago he had a sudden attack of severe precordial pain, radiating to the back, associated with cold sweat and collapse. The pain lasted one hour and gradually subsided. This was followed six months later by another similar attack, and a third attack three days ago. The last attack was associated

with extreme dyspnea, belching, cold perspiration and collapse.

Examination at this time revealed a markedly dyspneic male, with anxious look, tossing around from side to side due to marked discomfort. His color was ashen. The heart was enlarged to the left, rate 44, regular. The first sound was very weak and was replaced almost entirely by a systolic murmur heard best at the apex and transmitted to the axilla. The peripheral vessels were moderately sclerotic, pulse weak, and blood pressure systolic 120, diastolic 80. Previously, his blood pressure was over 200 systolic. The electrocardiogram (Fig. 30) showed 2:1 heart block. The auricular rate was 88, ventricular rate 44. There was left axis deviation. The S-T segment was depressed in the first lead and the R-T segment elevated in the third lead. The T wave seemed to be of the plateau-shaped type in the third lead, and negative.

## DISCUSSION

The clinical and electrocardiographic phenomena of acute coronary occlusion are dependent upon two underlying manifestations: (a) suddenness of onset, and (b) nature of damage.

### CLINICAL MANIFESTATIONS

*Suddenness of Onset*—What the determining factors are in the sudden onset of thrombotic or endarteritic occlusion of a vessel is still a debatable question. We can readily understand how sudden embolic occlusion might occur, but such being comparatively rare, we must still speculate on the causes of the sudden onset of the greater number of cases of occlusion. That it is the abruptness of onset, however, which is responsible for the greater part of the clinical picture is evidenced by the fact that chronic coronary occlusion with a gradual obliteration of as much as three-fourths of the

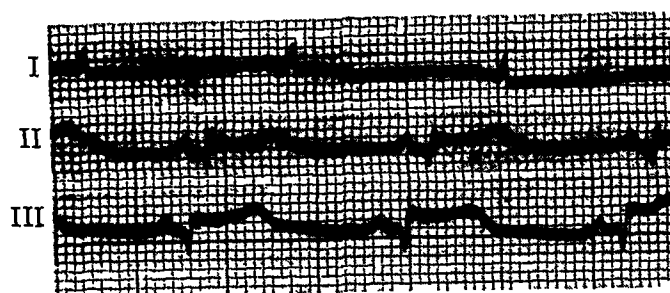


FIG 28

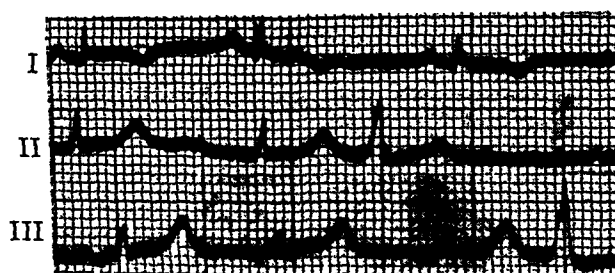


FIG 29

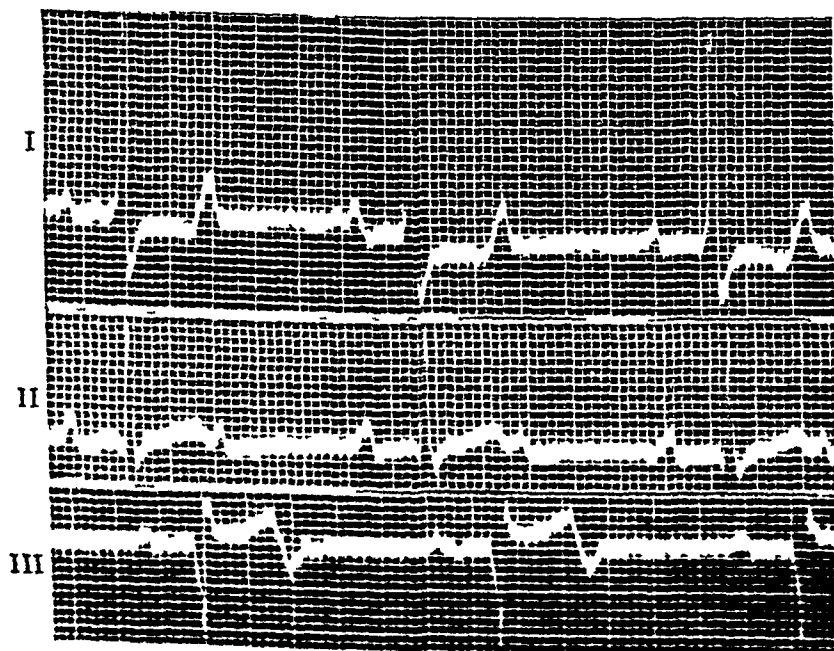


FIG 30



coronary system may occur with comparatively little discomfort, as shown by Osler<sup>1</sup>. It is of interest also to note that in many cases with typical symptoms of acute coronary occlusion reported by various authors, the post mortem examination did not reveal complete occlusion. A marked narrowing of a vessel by an atheromatous plaque with infarction of the portion of the heart supplied by that vessel were the usual findings in such cases. What determines the acuteness of symptoms is hard to tell. I would suggest the possibility of a sudden onset of edema in the vessel wall or in the intima overlying the atheromatous area, completely occluding the vessel during life and subsiding by the time the heart is examined, post mortem.

The acuteness of onset gives rise to a train of reflex phenomena which may be grouped under (1) so-called status anginosus or status asthmaticus of the European writers, and (2) shock.

Status anginosus is characterized by excruciating pain of variable duration of hours or days, usually situated in the retrosternal region, but it may be located mainly in the epigastrium, which some authors term "status gastralgicus," or it may be felt over the whole precordium. From its seat of greatest intensity, the pain may radiate to the left shoulder, left arm, both arms, back of chest, neck, left leg, or to two or more of those areas. In the twenty cases here reported, five had their greatest intensity of pain at the sternal region, five in the precordium, three in the epigastrium, two in the epigastrium and retrosternum, one in "both breasts." The radiation occurred in three cases to the left shoulder, in

one case to the left arm, leg and back, in one to the throat, in four to both arms, in one to the back between the scapulae, in one to the neck, in one to the neck and left shoulder, and in seven there was no transmission. In some of these there was no actual pain.

Instead of pain, there may be severe precordial or retrosternal tightness, marked epigastric oppression and gaseous eructation, or severe burning sensation in the precordial or epigastric region with nausea and vomiting. One of our patients complained of excruciating "heartburn" as if "hot smoke was rolling up from the stomach to the neck." Another complained of severe burning sensation in the epigastrium and throat, associated with pain in the shoulder. One experienced very severe epigastric oppression, and another, severe "tightness."

*Shock* is a second manifestation due to suddenness of onset. The marked reflex vasomotor disturbance produces a fall in blood pressure to an abnormally low level. This results in dyspnea, or even Cheyne-Stokes breathing, fainting, marked prostration, characteristic pallor or ashen color, marked sweating and coldness, weak pulse, feeble cardiac impulse and sounds, and the suppression of urine. That it is a reflex vasomotor disturbance, not the damaged heart, which is responsible for these manifestations—even the feeble cardiac impulse and weak sounds—is evidenced by the fact that many of these symptoms abate or diminish in intensity a day or two after the onset, at a time when the myocardial destruction is greatest. It is very likely also that it is the impoverishment in

the coronary blood supply due to the fall in blood pressure, which is responsible for the myocardial failure and the resulting signs of passive congestion, always present to a greater or less degree

*Nature of Damage*—This is responsible for the greater part of the objective phenomena which complete the clinical picture, as well as for the electrocardiographic manifestations

Infarction of the myocardium, resulting from coronary occlusion, gives rise to reactive processes — inflammatory, exudative and absorptive in nature — producing more or less fever and leucocytosis in the early stages. If the infarction extends to the pericardium, a reactive exudative pericarditis will result, producing the characteristic pericardial friction rub which is occasionally heard. The infarction more often reaches the endocardium, producing reactive endocarditis to which mural thrombi become attached. These may serve as emboli, and embolic phenomena are therefore frequent in this disease. Pulmonary embolism, resulting in pulmonary infarction, is most common. It occurred in two of our cases. The irritative and reactive processes of the myocardium also result in disturbances of rate and rhythm. The majority of cases show sinus tachycardia. In some cases, such as 19 and 20 of our series there is a marked bradycardia. This gradually mounts to normal with improvement, as in case 19. The bradycardia may be of sinus origin or due to block. In the latter case, the auricular rate may be rapid. Occasionally the disturbance in conduction is transient in which case it

is most likely due to edematous infiltration around the conducting system, which subsides. Gallop rhythm is a very frequent finding. Of the arrhythmias, the most common are premature contractions, but flutter, fibrillation and paroxysmal tachycardia were observed

#### ELECTROCARDIOGRAPHIC EVIDENCE

In a person past 30 years of age, with sudden onset of the characteristic anginal syndrome, fainting, marked fall in blood pressure, characteristic color, muffled heart sounds, with perhaps, gallop rhythm and various forms of arrhythmia, followed later by some rise in temperature, leucocytosis, and possible pericardial friction rub, the diagnosis of coronary occlusion may be made with certainty. We have, however, the additional help of the electrocardiogram

In 1909, Eppinger and Rothberger<sup>2</sup>, described the alterations in the QRS and T waves caused by destroying part of the left ventricular musculature by silver nitrate. A current of injury was set up resulting in a monophasic curve. No definite T wave was evident, but the R-T segment rose high on the descending limb of the R wave and came down in a curved fashion to the isoelectric line. As repair of the damaged muscle took place, the R-T deviation gradually came down to the isoelectric line, and a definite T wave was formed

In 1918, Smith<sup>4</sup> produced experimental occlusion of the coronary arteries by ligation. The electrocardiogram showed fairly constant T wave changes, from markedly positive soon after ligation to markedly negative in about 24 hours. This was followed by an iso-

electric T wave which again became positive on about the seventh day. The size of the positive and negative phases as well as the height of the R-T interval were in direct proportion to the size of the artery ligated. At the end of four weeks, the T wave again became isoelectric or negative in one or more leads.

In 1920 Pardee<sup>4</sup> described similar T wave changes in a clinical case. Early there was a high R-T level, followed by its gradual lowering and rounding, and final production of a negative T wave. The R-T deviation has since been labeled "Pardee's Coronary Occlusion T wave."

In the same year, Smith<sup>5</sup> showed that the greatest negativity in the T wave occurred in those dogs where the blood supply to the apex was affected greatest. He reported three years later<sup>6</sup> the electrocardiographic findings of 11 patients with coronary occlusion where the T wave changes were similar to those of experimental occlusion.

Weain<sup>7</sup>, on the other hand, in a series of 19 autopsy cases of coronary thrombosis and myocardial infarction, found only one record with typical R-T changes. The other electrocardiographic findings were those of premature contractions, block, auricular fibrillation, delayed QRS conduction, and in two cases, perfectly normal curves. His conclusions were that "no one form of electrocardiogram is characteristic of this condition." He adds, however, that no definite conclusion can be drawn from his series, as there was a variation in time of relationship between the onset and record taking, in the different cases.

Parkinson and Bedford<sup>8</sup>, analyzing the electrocardiographic tracings of 100 cases of coronary thrombosis, found deviations in the R-T and S-T segments occurring early in most cases, and a negative T wave followed later. The R-T and S-T elevations and depressions were best seen in the first and third leads, and were opposite in direction. The T wave in some cases became evident before the R-T segment returned to the iso-electric line, in which case the direction of the T wave was always opposite to that of the R-T segment. The authors believed that if the R-T deviation lasted several weeks, it pointed towards the extension of the infarct—the usual duration being one week. They divided the T wave changes into "Type One," where it is negative in the first lead, or in the first and second leads, and "Type Three," where it is negative in the third lead or in the third and second leads. They further added that there may be atypical T wave changes such as inversion in all leads, or a normal T wave, which may be due either to recovery or to infarction occurring in a "silent area" as far as the T wave changes were concerned.

Barnes and Whitten<sup>9</sup>, in twenty-one cases with "Type One" T wave, found the infarction to occur in the anterior and apical portion of the left ventricle, in the region supplied by the left coronary artery. In six cases with "Type Three" T wave, infarction occurred in the posterior portion of the left ventricle, in the region ordinarily supplied by the right coronary artery. In four cases of the mixed type, infarcts were found in both, the anterior

and the posterior portions. Shifting type indicates new infarction.

In the cases presented in our paper, seven showed definite R-T elevation or rounding in the third and second leads, with corresponding depression in the first lead. In all these cases, the T wave was fully developed, and was of "Type Three." In two of these, the R-T segment was still above the isoelectric line four weeks after the onset, and no clinical evidence of extension of infarction was present. In another case (Case 13), such deviation was present nine months after the onset. The electrocardiograms of four other cases approached the "Type One" T wave, although not typically so in all cases. One of these (Case 18), showed some depression or rounding of the S-T segment in the first and second leads two years after the onset, but there is reason to believe that he had fresh myocardial infarction at the time the tracing was done. Case 19 showed a high R-T segment in the third and second leads but the developed T wave was not opposite in direction to the R-T segment.

The remaining nine cases of our series did not show any typical R-T or S-T deviation, and no constant T changes. Case Four, for instance, had the R-T and S-T segments above the isoelectric line in all leads. Case Six, showed practically no elevation or depression of the R-T segment three days after the onset. Ten weeks later, however, during which time he felt quite comfortable and the physical findings were negative he showed some depression and rounding of the S-T segment in the second and third leads

a lower T wave in the first lead and a negative T wave in the second lead.

Case Fourteen showed a high S-T segment in the third and second leads, with a markedly accentuated T wave in those leads, and a negative T wave in the first lead, four days after the onset. Seven weeks later, there were positive T waves in all leads and, except for the axis deviation and some slurring of QRS, the tracing appears perfectly normal. I feel, however, that this is merely an intermediary stage, and that he will develop a "Type Three" tracing.

The other findings of note are (a) Very low voltage QRS complexes in Cases Twelve and Nineteen, with increase in such voltage in Case Twelve, on improvement. (b) Extremely deep T wave in Case Five, becoming less so as the patient improved. (c) Auricular fibrillation, Case Three. (d) Diminished height of the R wave in the third lead and depth of the S wave in the first lead in Case Two, two weeks after the first tracing. (e) Change in the electrical axis from left to right, in Case Nine. (f) First and second degrees heart block, in Cases One and Twenty respectively.

The conclusions we may draw from our electrocardiographic findings, as well as from those of the references mentioned, are that although the so-called "Coronary Occlusion T Wave" may be considered to be pathognomonic when present *in association with a typical or somewhat atypical clinical picture* of coronary occlusion its absence does not rule out such occlusion, for it is more frequently absent or anomalous than present. Furthermore its presence is not always indicative of

coronary occlusion, as it has been found in such conditions as rheumatic myocarditis, by Cohen and Swift<sup>10</sup>, in rheumatic pericarditis, by Poite and Pardee<sup>11</sup>, and, in massive pericardial effusion, clinical and experimental, by Scott, Feil and Katz<sup>12</sup>. It is at best a finding of peculiarly localized myocardial damage, due to occlusion if the clinical picture points towards that condition, at which time it is conclusive evidence.

I would consider the most important electrocardiographic evidence of coronary occlusion the *frequent alterations* in the make-up of the electrocardiogram, in periods of days or weeks. Of these the most significant are the changes in position and configuration of the R-T and S-T segments and the T wave. Of the latter, its exaggerated height, followed by gradual depression and final negativity, are significant. Significant also are the alternate negativity and positivity of the T wave in various leads from time to time, during comparatively short intervals, during some phases of which the electrocardiogram may even appear to be perfectly normal, and rather misleading in the diagnosis. Repetition of the tracing, however, at a later time will give us the true state.

Other significant changes from time to time are (a) High voltage QRS waves followed by markedly low voltage, which again increases later, (b) Change in the direction of the electrical axis from left to right, and vice versa, (c) Appearance and disappearance of block, (d) Appearance and disappearance of premature contractions; (e) Variations in the heights of the various

components of the QRS complex from time to time.

These findings and changes are well demonstrated in our cases, as well as in two cases reported by Willius<sup>13</sup>, and in the experimental and clinical cases reported by the authors quoted elsewhere. If no other electrocardiographic evidence is found, the frequent alterations of whatever complexes are present may be considered to be pathognomonic. Acute myocarditis, of rheumatic or other infectious origin, may also produce frequent changes in the electrocardiogram corresponding with the spread of the inflammation, its localization, and its subsidence. The clinical picture, however, as well as the age of the individual—occurring usually in earlier life—will help us in the differential diagnosis.

#### SUMMARY

Twenty cases of acute coronary occlusion are reported, and the clinical manifestations as well as the electrocardiographic findings are discussed.

The clinical and electrocardiographic phenomena are dependent on the acuteness of onset, and the character of the damage. The former gives rise to the anginous syndrome and shock, with its concomitant manifestations. The latter is responsible for the objective phenomena, such as fever, leucocytosis, pericardial friction rub, embolic phenomena and electrocardiographic changes.

The outstanding features of the electrocardiogram are the frequent changes in the configuration and level of the R-T and S-T segments, and the configuration of the T wave. Less

frequent, but equally important, are variations in the height, conduction time and configuration of the QRS complex, changes in auriculo-ventricular and interventricular conduction, and in the direction of the electrical axis, at various times in the course of the disease. Emphasis is to be laid on changes in the components of the electrocardiogram, rather than on any single finding no matter how significant it may be.

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# A New Esophageal and Cardiospasm Dilator

By MOSES EINHORN, M D, *New York*

CARDIOSPASM has been defined as a spasm of the musculature of the cardia or epicardia sufficient to cause either partial or complete obstruction to the passage of food from the esophagus into the stomach. The subject of the treatment of this condition has occupied the attention of clinicians throughout the world, and the only effectual results were obtained by a series of intermittent dilatations by means of rubber balloon dilators operated by hydrostatic or pneumatic pressure. Some, particularly Starck<sup>1</sup> and Schreiber<sup>2</sup>, have preferred using mechanical divulsors, inserted through the esophagoscope, under the guidance of the eye and the sense of touch.

Bougienage was for some time employed, small bougies first being introduced, and gradually increased to the largest size. The bougies were left in position and in contact with the stricture, and drawn frequently through the cardia, at each treatment. Leyden successfully employed permanent cannulas, which remained in situ for several days. These cannulas were introduced with the aid of the stomach tube. They were from six to eight centimeters in length, and were attached by means of strong cords to the ear or around the neck.

In latter years, dilatation by air and water has been advocated, as suggested

by Plummer<sup>3</sup>, Sippy<sup>4</sup>, Mosher<sup>5</sup>, and Vincent<sup>6</sup>. These dilators are similar in construction, consisting of a long rubber tube, 34 French in diameter, with a conical metallic acorn at the lower end. Several holes are perforated within a few inches of the bottom of the tube, and this section of tubing is encased in a rubber bag, covered with another silk or linen bag, and an additional layer of thin rubber. A silk thread is used in some of these dilators, as a special means of guiding the metallic acorn through the cardiac orifice. Zohlen<sup>7</sup> introduced a flexible dilator with a series of expansible olives, but judging from the description, the apparatus appears rather complicated in structure.

Surgery as a means of treatment was employed with successful results, by numerous surgeons including Mikulicz<sup>8</sup> and Erdmann<sup>9</sup>. Gastrostomy was usually performed, followed either by digital dilatation of the spasmodic area from below upwards, or by introducing long curved forceps, the blades, covered with rubber.

In a recent article<sup>10</sup>, I advanced gastric feeding as a new treatment for cardiospasm, and had great success with same in the treatment of patients suffering with a mild degree of esophageal spasms. In this treatment, I use my new gastroduodenal apparatus<sup>11</sup>, which consists of a special bucket

and a marked tube. The main characteristics of the bucket are its three part composition, its capsular shape, spiral arrangement and its lower part three times heavier than the upper part. The patient is fed with the aid of the tube for a period of ten days, and during this period, remains in bed with the inserted tube, in order to insure complete rest and relaxation. The treatment, may however, be ambulatory. Every three days, preferably in the morning, on an empty stomach, the tube is removed for cleansing purposes. It is first removed but a few inches, and the saliva which has accumulated in the esophagus above the spasmodic area is withdrawn with a syringe. The esophagus is then thoroughly washed, by injecting a solution of boric acid or luke warm water through the tube. After repeating this process several times, the tube is removed, cleansed with warm water, and re-inserted into the stomach.

The feedings should be frequent and in small quantities, not exceeding one and a half ( $1\frac{1}{2}$ ) glasses every two or three hours. Sharp and spicy foods should be avoided, also, extremes in heat or cold. Water may be taken through the tube between meals, and thirst and dryness of the mouth satisfied with the aid of a mouthwash. The diet consists of orange juice, grape juice, tea, cocoa, chocolate, coffee, milk, cream mixture, ( $\frac{3}{4}$  milk,  $\frac{1}{4}$  cream), tea and milk, egg-nog, farina, vegetable soup, celery soup, asparagus soup, chicken soup, barley soup, gruel, beef juice, spinach (liquid form), jello, custard, apple sauce and fruit sauce.

The above treatment offers the following advantages:

1 Complete rest is offered to the spasmodic area, including the lower part of the esophagus.

2 The patient is free from discomfort, in the epigastric region, usually accompanying cardiospasm.

3 The intake of food can be increased with the aid of the tube, and weight incidentally gained.

4 Physical and psychic rest obtained by this treatment indirectly has a beneficial effect on the cardiospasm.

5 The constant presence of the tube at the site of the spasmodic area, tends to counteract the spasms.

In certain cases, however, gastric feeding is insufficient in the treatment of cardiospasm, and intermittent dilatation by special instruments is often necessary. I had occasion both here and abroad, to use the numerous devices heretofore mentioned, but in each case I found the same mechanically unsatisfactory. Besides being bulky and uncomfortable for the patient to retain, the danger of perforation of the esophagus was encountered in the use of these appliances.

I observed particularly, in my study of cardiospasm, that the spasms were usually unequally distributed, and that the highest degree of spasticity was generally present at the cardiac opening. I was also impressed by the excellent results obtained by surgeons in manual dilatation of the cardia from below upwards and laterally, and therefore concluded that in order to dilate the spasmodic area mechanically, the strength of dilatation should be applied from below upwards and laterally, and not from above downwards. As a result of this observation and study, I



devised an apparatus on the basic principles of lateral and retro-dilatation

My cardio-dilator apparatus (Fig 1-A), consists of a special bucket, a tube, a rubber bag, and a syringe. The bucket (Fig 2), is one inch in length, 11 grams in width, and 27 French in diameter. It is of capsule shape, with an obtuse point and is composed of three divisions: (a) neck, (b) shaft, (c) bottom.

#### A The Bucket

(a) The neck, through which a large opening is bored, serves as an outlet to the hollow chamber at the bottom of the bucket, to which the tube and small rubber bag are attached.

(b) The shaft has a groove  $\frac{1}{8}$  inch in width, to which the rubber bag is fastened. A canal drilled through the

shaft, connects the neck with the bottom of the bucket.

(c) The bottom, consists of a hollow chamber, which contains four openings for the passage of the fluid. This perforated chamber is connected to the neck by a large canal drilled through the shaft. A wire, soldered at one end to the bottom of the bucket, passes through the canal and the neck, and extends the entire length of the tube. The wire is soldered to a small metal connection at the outer end of the tube.

#### B The Tube

The tube (Fig 1-A) is 12 French in diameter, semi-soft in quality and is 28 inches in length. It is marked off by a heavy black line 24 inches from the bucket. At the outer end of the tube is a small metal connection, to

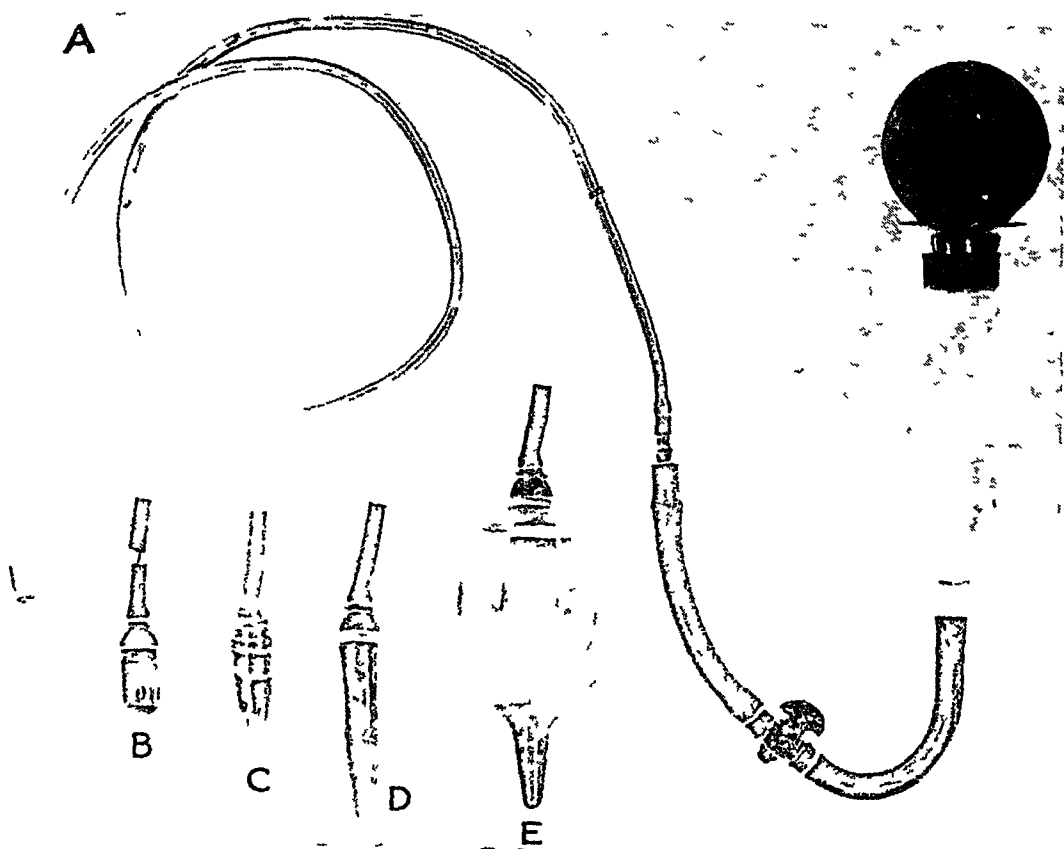


FIG 1



FIG 2

which the wire which passes through the tube is soldered. Two additional pieces of rubber, separated by the insertion of a rubber stop-cock are connected to the tube at this point. The rubber stop-cock is introduced to regulate the flow of the fluid through the tube and into the bag. The wire which extends through the tube, reinforces it, and tends to supply the resistance necessary when force is employed to overcome the spasmodic area, and also to withdraw the bag in the process of retro-dilatation.

#### C *The Rubber Bag*

The small rubber bag is  $2\frac{1}{2}$  inches in length, conical in shape and fits over the bucket, where it is securely fastened with a silk thread at the neck and the groove. It possesses special elastic qualities suited for the purpose, and can be dilated to the extent of  $2\frac{1}{2}$  or more inches in diameter.

#### D *The Syringe*

The syringe, used with the apparatus, should be of large size, and preferably graduated.

#### *Method Employed*

Prior to introducing the apparatus, the small rubber bag is inflated with air and gently folded back over the bucket (Fig 1-C). The patient, who has been instructed to report on an empty stomach, is placed in an upright position on a chair and is ordered to

open his mouth. The bucket, which has been previously moistened, is held between the operator's thumb and forefinger, the middle finger being used as a base, and is placed on the tongue of the patient. After the bucket has been balanced, the patient is instructed to utter the sound AH. The tube is pushed quickly, and the patient concentrates on the act of swallowing. Due to its weight and capsular shape, the bucket will slowly be carried down through the esophagus to the spasmodic area. The tube is then swallowed to within three inches of the mark, and if resistance is encountered, the operator, holding the tube and wire taut, forcibly presses same forward, overcoming the spasmodic area. The tube is now swallowed until the mark is reached, and the patient is fluoroscoped, the various steps in the process of dilatation being carefully followed.

When the tube is observed to have entered the stomach (Fig 3), a little air is injected through the syringe, causing the folds of the rubber bag to slip down from the bucket (Fig 4 and Fig 1-D). The syringe is removed and filled with a mixture of barium, about 4 cc of which is injected into the tube, inflating the bag to about the size and shape of an egg (Fig 5 and Fig 1-E). The stop-cock is immediately closed to prevent the return of the barium to the syringe, and the tube is withdrawn until the cardiac sphincter is encountered and resistance is felt by the patient. A piece of adhesive tape, indicating the distance from the mouth to the cardiac opening of the stomach, is attached to the tube at the point of contact with the mouth.



FIG 3



FIG 4

The stop-cock is now released and a little of the fluid is returned to the syringe. The dilating bag is thus decreased in size, and retro-dilatation is commenced, gentle and continuous traction being applied to the tube and the wire. Slowly the sphincter begins to yield to the wedge-like action of the rubber bag, permitting the upper part to pass through the spasmodic area. By pushing the tube the rubber bag is slipped back into the stomach. The stop-cock is then released, a little more of the barium is injected, and the process of retro-dilatation is repeated.

In order to dilate the spasmodic area laterally, the barium is again siphoned into the syringe. The tube is then withdrawn about an inch, bringing the rubber bag directly in the spasmodic area.

About 2 cc or more of the barium is injected, and the rubber bag is inflated, producing lateral dilatation. The procedure is usually accompanied by pain, if pain is not felt by the patient, the rubber bag has either been insufficiently dilated, or has probably slipped back into the stomach. The bag is allowed to rest at the spasmodic area for a period of five minutes. When the dilatation becomes too painful, part of the barium is withdrawn in order to reduce the size of the inflated bag. This process is continued for a period of 20 minutes, at five-minute intervals, and should be repeated every three days.

Fluoroscopy is necessary only during the first dilation, to determine the length of tubing to be swallowed in order that the dilating bag extends be-



FIG 5

yond the spasmodic area. Thereafter, the exact location is ascertained by the markings on the tube, the degree of dilatation being measured by the cubic centimeters of fluid injected into the dilating bag.

### *Advantages*

- 1 It is simple in construction, inexpensive and not bulky
- 2 It is easily swallowed without trauma to the esophagus
- 3 No danger of perforating the esophagus
- 4 It can be comfortably retained by the patient for some length of time

5. The use of a silk thread guide is eliminated, as the bucket acts as a guide

6 Air and water pressure gauges are eliminated

7 Lateral and retro-dilatation can be accomplished

8 The degree of dilatation of the rubber bag is ascertained by the volume of fluid injected from the syringe into the dilating bag

9 It is simple in technique, and can be readily operated both by the physician and the patient

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## Pertaining to Peptic Ulcer\*

By ANTHONY BASSLER, M D, *New York*

ONE hundred years ago Cruveilhier showed that gastric ulcer was a clinical entity. Before him (in 1793) Matthhew Baillie wrote about it, and patients complaining of it were described in the 16th century. Thus for 300 years something was known about it, this knowledge for 100 years more fully employed, and in the last 25 years most intimately, and yet really nobody knows much of anything about it. Someday, somewhere, somebody is going to tell us accurately what peptic ulcers are caused by, and then we are going to know something worth the while about it, and get somewhere with it. When you have 15 causes for a disease or a condition, the rule is that none of them is right, and until the etiology is known, we are going to be divided into those who do not think, those who think they think, those who think wrong, and those who think.

Regarding symptoms we also are in a chaotic state. In one out of every three new patients I see in my office a diagnosis of ulcer had been made, most of them in a definite way and in a few strongly suspected. Of these about one in twelve have an ulcer in my opinion. There is no condition in

medicine in which jumping at diagnosis is more of a continuous hurdle race. Some believe that all you need is an X-ray examination to make a positive diagnosis. Others, like myself for instance, claim this not to be of such value (and might even be misleading) unless there is a history which is suggestive, and unless in deducting from the history and the examinations one constantly remembers that quite perfect ulcer syndromes are present in gall-bladder and appendix disease, upper abdomen adhesions, gastric hypersecretions and mucosal sensitiveness, and some other conditions from which differentiation is essential. To me to make a correct diagnosis of ulcer, especially gastric and lower esophageal, is a difficult matter. Duodenal is much more easy. There are many roentgenologists, practitioners, surgeons, and even gastro-enterologists who diagnose or suspect ulcers far more often than they exist. Contacting such, the patient pays his money and takes his chances, because the average patient, with his or her limited knowledge of medicine, to mention the word "ulcer" is something readily understood, not a few have had told them or suspect that it leads to cancer, so it's a good kind of a financial proposition of practice, and if such a man is literarily inclined his statistics of cure are very

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fine, very fine indeed. Now, if we are going to get anywhere worth the while on this subject, an ulcer either exists or it does not, and there should be no twilight diagnosis lit with question and shadowed with doubt. In analytical thought and examinations, the constantly varying clinical picture of this disorder in incidence of pain and measures of its relief, tenderness on pressure, absence or presence of vomiting and its character, bleeding, the X-rays, gastric analyses, and what pertains to penetration, perforation, obstruction, etc. must all be interpreted pivotally as to the diagnosis and relatively as to other conditions which can cause like symptoms and findings. Manifestly, unless all examinations are carefully made, fully done, and wisely evaluated, statistics of neither incidence nor treatment are worth much. In this ulcer question the best of us are only half good enough, and none of us should tickle himself with the vanity of a Roman of being his own God in accuracy, and this applies more for the medical man than the surgeon. Unless in the diagnosis one has proof enough to be sure, so far as ulcer in the science of medicine is concerned, in the words of Moran and Mack it would be better if he "hadn't mentioned it."

Then again no two men agree on much of anything in treatment. There have been advanced 28 different ulcer diets, and they in character and kinds run all the way from animal crackers to the inmates of a zoo. One feeds by rectum to do away with foods irritating the stomach, the next uses a duodenal tube to accomplish the same purpose, and then the next advances, what is popular today, feedings every two

hours with foodstuffs of high caloric values to give the stomach lots to do. One claims that to give alkalis is a gross mistake, the next uses little doses of them, and just as good men push the alkalis to the very limit. Long presentations are made on these matters which are about of as much value as porcupine quills on a kangaroo's back. Some state that only the best treatments are of any value, and others are not insistent on it, and some even, like myself, feel that the ambulatory method in a conscientious patient is often the one of choice. Long discussions, realms of paper, nightly meetings are devoted to these points which are like drops on a window-pane, they run together and trickle away. There are some who believe the subject almost totally medical, with others it is almost totally surgical. Largely the advice given to the patient is tinctured according to the inclination and interests of the doctor. If he is a medical man he visualizes it as a matter of treatment, if a surgeon a matter of operation. Unlike Dean Swift "one ignores the other's bill of fare and yet does not pay the bill of the company."

Now with all these inconsistencies you have asked me to present the subject of the medical treatment of ulcer. How can I do this unless simply to tell you what I do with this condition, and I am probably as much right and wrong as anybody.

In the first place I must be absolutely sure that an ulcer is present. This being so, I search for focal infections in the nasal and paranasal sinuses, throat, mouth and teeth. I may demand that these be attended to before I go any further, or that they be attended

to on the way On the basis of how long the symptoms have been present, the location and size of the ulcer, in the absence of frank surgical cases and complications, I note whether there is a positive Kahn test, consider the existence and status of anemia, the economic environments of the patient, and consider whether the patient would be best off in bed for three or four weeks, be treated up and around, or operated upon at once If there is a notch present and it is deep or broad, I occasionally advise bed handling, the same being so in the hemorrhage and secondary anemia cases, and those with bad status of nervous system Since these comprise only the smaller number of the whole, the ambulatory method is usually followed, and if for any reason they cannot go to bed, I am willing to go ahead with the up and around plan

In the bed plan, I start with a clearing out of the bowels with calomel and Carlsbad salt, never any other saline because that's the only alkaline one there is, and is one I may advise taking occasionally on the way though For 24 or 36 hours no foods are taken, small doses of alkalis given while the starvation is on A reasonable bland diet is ordered with foods taken at three or four-hour intervals, for the first ten days this being totally fluid, and finely comminuted foodstuffs after that Bathroom privileges are allowed, a Priesnitz or sweat bandage is used for pain (never any opiates) or perhaps a lamp for hourly doses With the feedings I start with the usually overworked Sippy powders, using the bismuth or the magnesia ones according to bowel movements As a rule

I start with more of the bismuth than the magnesia and usually have to wind up with more of the magnesia Three times a day the pH of the urine is taken, this being more accurate in the fine gradations of reaction than litmus papers Any nurse can do this on five minutes instruction In quantity and size, the powders are given during waking time according to the reactions of the urine, the point being to get the urine just short of pH 7 and never allowing it to become more alkaline than this The powders are increased until this is accomplished These tests of the urine compared to the original one and the ones on the way along suggest how much alkali to employ If the urine, and that means the stomach, too, persists in acidity you can follow the Sippy suggestions in doses, but in nine cases out of ten this is not only unnecessary and unwise but bad therapeutics in addition Ulcers do not heal well under states of alkalosis, the patient's complaints are a nuisance when toxic symptoms are on, the whole treatment is upset, and it's difficult to get patients quiet again for days Occasionally belladonna or atropine in small doses is employed, and, of course, a positive or questionable Kahn test adds mercury or the arsenicals hypodermically to the routine

For the first month out of bed only milk, cream, cereals, bread and butter, simple cakes, jello and such are allowed In a sense you go back to a more simple dietetic plan than that used at the end of the bed treatment These foods are added to in the second month, and as I have originally advanced more or less dieting in kept up for six months with alkaline pow-



ders, iron injections, as much rest as possible, perhaps olive oil before meals when the acidity is high and the general condition poor, and in all instances small doses of mercury bichloride and arsenic trioxide three times a day. The stomach is X-rayed each month and the films matched. At a satisfactory result the patient is discharged for the time being with a list of especially irritating foods they must not eat, and told to return if the symptoms recur.

If the X-ray findings or the clinical course do not satisfy me, I suggest an operation at any time. This is the routine treatment even when hemorrhage is or has been present, excepting that morphine and complete physical rest are used in frank bleeding (and morphine is better than all the coagulating blood preparations that ever were advanced) with perhaps the cautious use of blood transfusions. Immediate operation is never advised to control hemorrhage, except when perforation is also present. Sometimes careful lavage with ice water and the administration of four c c doses of adrenalin solution are employed.

Everybody agrees as to the value of bed treatment, claiming that as the nervous system is quieted, gastric motility and secretion are controlled. I believe there is some value to it at times, but I doubt that the results compared to the ambulatory treatment are anywhere as great as is believed. With all the other disagreements on this subject it seems poor grace on my part to disagree in any way with the one thing that practically everyone believes in, but we have now handled over 400 cases of gastroduodenal ulcer by ambulatory methods and over 300 by bed

treatment, and, after two years time, compared the results in both groups. Figuring especially incidence of operation and return of symptoms, the statistics can be made to show four per cent in favor of the bed method. But these bed cases were a straight line of instances in a period when practically all cases were treated that way, and in them were many more of the milder types than are handled by bed methods today. If these are taken out of the statistics and recomparisons made, the difference is between six and half a dozen. Up to a few years ago, I felt that patients who could not afford to go to bed should preferably be operated upon. After I had a hundred or more walking around with ulcers, not a few supporting families at hard working jobs, and I saw the results accomplished, they taught me that I was wrong in the average case of ulcer and that it was best to try it out their way, and if they had to go to bed, to have an operation as the reason why they went there.

When handled in the ambulatory way, restrictive dieting is not practical. The patient is started with the same food plan as the first month out of bed, and followed for six months just the same. They are taught the litmus paper method of testing urine, alkalies are given according to the reactions, and all of the procedures of the bed treatment are employed. As much physical rest as possible is insisted upon, the Piessnitz or sweat bandage or the lamp being used in the evenings and during Sundays and holidays. X-rays and matching of films is done once a month, the use of tobacco is stopped, exposures to taking colds guarded

against, and the general condition of the patient bucked up as much as possible. As I advanced in 1910, one or two therapeutic doses of x-ray is given over the entire stomach each week for about ten times. This is begun after the bed treatment, or after the second month in the ambulatory. This serves to diminish the running status of acidity, hypermotility and spasm, and to produce a softer, smaller, and more resisting type of scar. Unless operated upon in the interval, observation is continued for six months time. Not a few of the largest and most persistent ulcers have done well on this up and around method.

In 1910 when the Mayos were teaching their belief that all duodenal ulcers were chronic and should be operated upon, and the whole surgical world agreed with them, I claimed in the first edition of my text book on the stomach that about one-third accomplished satisfactory results by medical means. Now I desire to raise this figure, as deducted in three hundred and twenty-four cases studied after two years of termination of treatment, to practically 50 per cent. This figure, while still not quite as high as in gastric ulcer, is high enough to warrant a trial of medical treatment in duodenal ulcer as well as in gastric.

Another point is that my experience is the same as others in that gastric ulcer has almost no connection with carcinoma and duodenal ulcer positively none. Here and there one has occurred but in incidence it is not even up to the medical man's allowance of five per cent. Practically all ulcers that become malignant are potentially or actually correct with ulceration at the

start. One cannot always discern this, but when a case has been on medical treatment for a month or two, as a rule, the X-ray re-examinations and checkups will tell quickly enough whether there should be a continuation of the medical treatment or a resort to surgery. What plan is simpler or more practical than this? I feel distinctly that in those patients who had an ulcer and years afterward develop a cancer, who knows whether it came from the ulcer or started independently of it? Nobody, and neither the gross nor microscopical findings can prove it.

It has been said that there are five indications for surgery, these being perforation, hemorrhage, obstruction, carcinoma, and utter failure of medical treatments. Well, I am not so sure about these as is my friend, the conservative surgeon, Dr Frank Leahy of Boston. In perforation and carcinoma I agree totally. My attitude on frank hemorrhage has been mentioned. The recurrent type in surgical significance is often dependent upon conscientious effort in following medical treatment, how much it produces anemia, and the incidence of more frank bleedings. In certainly about a third of the cases it stops even though it had persisted for weeks or months of time. To me, the length of time of bleeding is not as important a factor for surgery as is its effect upon the body from the anemia and the recurrences of distinct bleedings.

Increasing experience has shown how frequently a pyloric obstruction caused by an ulcer is due to edema, congestion and interference with the normal relaxation of the pyloric sphincter. With the healing the ob-

struction often disappears. If it persists it is due to cicatricial contraction because a fibrous stricture is generally the result of many years of alternating activity and partial healing. By pyloric obstruction here is meant large retention after twelve hours, not the usual 6 or 7 hour X-ray kind. I have had not a few almost total retentions for 24 hours with enormous dilatations of the stomach and vomiting suddenly relax and the whole obstruction quickly disappear and not recur.

Regarding utter failures from medical treatment, these comprise a group of cases in which opinions must be based upon conditions concerning the patient, the type of treatment followed, and how long they were kept up. It is interesting to have operation advised because of failure of medical treatment when in reality there had been none. On this point my observations have often been about like this. An individual with a suspicion of ulcer present in the history is promptly sent for X-ray examination, nothing more being done or considered. The X-ray man reports an ulcer and then the advice is given according to the inclinations of the physician as to whether he is a medical man or a surgeon. Attitude of departmental interest in medicine is expressed which is largely personal, when it should be entirely that of the subject and patient's interest, because after all in the non-tragic ulcer case, as a rule, the patient cerebrates considerably about it, is liable to take quite an analytical interest in his ulcer, and may shop around for opinions and advice. What is especially irritating are those statements of failure of medical treatments when only an oc-

casional dose of bicarbonate of soda had been taken. Now there is an interesting side to this that is when the surgeon himself has an ulcer, and I have seen several. He seems to care a good deal about the thing and always gives time, care, and judgment that medical procedures are given a fair chance.

Another thing I notice about the medical man when operation is contemplated on him that he is not very keen about a rather extensive partial gastrectomy being done on him. I wonder why? Great effort is being made and reasons are being given why it is the one really good thing to do. Here's my experience. If you take 100 ulcer cases you get along satisfactory well in about 75 with medical handling. In the remaining 25, the well known operations of the past will fix up about 15. About two will die from the operation, and that leaves about 8 in which the patient, the doctor, and the surgeon all together become gracefully suspended between Heaven and Earth. Some are treated medically again and an occasional one really cleans up by this combination. Some are reoperated, and I feel sorry for the surgeons in this group. Like the poor relative, they hang around. Now of course, if these are the ones who are resected—fine. But to resect in a wholesale or general way, just because an ulcer is in the stomach, had been there for some time or because surgery had failed in many cases in the past, in my opinion, never will be fair or become popular. It is a procedure for the ulcer derelicts, and with it some of these can be reclaimed. My advice in a general way with the

treatment of ulcer is to step along slowly, calmly, yet firmly Surprises are always happening, and many of our best-arrived-at opinions are only those of conviction Practically all of my own mistakes in cases have come

when I took a definite stand and I had not had the time for good judgment, or when I did have the time, I did not exercise it Conviction! Why? Because I still do not know what causes it

# Lambliasis Simulating Duodenal Ulcer

## CASE REPORT

By EDWIN BOROS, M D , *New York*

**T**HE symptomatology of duodenal ulcer and its response to the customary medical and dietary treatment is often regarded as sufficient evidence for its diagnosis, despite the frequent absence of other confirmatory laboratory or roentgenological data. This so-called characteristic picture of duodenal ulcer may, however, be mimicked by other conditions, one of which presented itself with a similarity of symptoms.

Mrs H M , married, age 43, having two children aged 18 and 14, without history of menstrual disorders or miscarriages, dated the onset of her trouble back 3 or 4 years ago, when she noticed a diarrhea as a first symptom of ill health in a past which was strikingly free from any illnesses or operations. Her discomfort was described as an intermittent watery diarrhea of one or two days duration, which announced itself as a series of cramps about the navel which soon disappeared. The infrequency of these attacks and their attribution to indiscretions of diet, relegated medical consultation to such a time, when about one year subsequently, a new series of disturbances manifested themselves, characterized by a bloating and pressure feeling in the pit of the stomach rather constant in duration. Simultaneously severe cramps about two hours

after the intake of food were experienced which radiated to the right hypochondrium and back. These latter pains seem to be relieved by the application of a hot water bag and the eating of some crackers and were periodic in their occurrence. Jaundice was never observed. There was a loss of about 8 pounds in weight since the onset of the first diarrhea, despite a relatively normal appetite. The occurrence of severe cramps in the early morning hours and the failure of relief subsequent to the institution of a strict medical and dietary regimen, prompted the patient to appear, at which time she presented the following findings.

The patient was a well developed and nourished female, weighing 148 pounds, with respiration, pulse and temperature normal. The eyes, ears, nose, throat and glands revealed no disease. Examination of the chest was negative. The abdomen was scaphoid and a moderate amount of tenderness was present in the epigastrium. The superficial head zone in the right hypochondrium showed an excessive response to pressure. No mass, splenic or hepatic enlargement was disclosed, but there was a spastic cecum which rolled distinctly under the fingers together with a similar feel at the sigmoid. A gastric analysis was decided upon. The Ewald meal showed a free

acid of 35 and the total acid was 50. Fluoroscopic examination presented a hypermotile stomach with hyperperistalsis and a high secretion level. No ulcerations were found and the duodenal cap was free from any visible pathology. The blood findings were essentially negative, as was the stool. The secretions obtained by duodenal drainage dramatically demonstrated the presence of active motile forms of the *Lamblia* parasite, which were similarly present in the bile. Subsequent stool examinations were negative, until a fresh warm specimen finally presented active motile *Lamblia*.

A course of intravenous injections of 45 grams of neosalvarsan, at five day intervals was given, with an immediate amelioration of symptoms, and a total disappearance of the parasites after the fifth injection. Subsequent stool and duodenal specimens covering a period of four months failed to reveal the existence of the *Lamblia*, and there ensued a complete restoration to normal health.

#### COMMENT AND SUMMARY

Infection with the *Lamblia* parasite is apparently not as uncommon as is

generally thought. Numerous cases have been reported, the first one, in N. Y. State by DuBois and Toro<sup>1</sup> in 1912. Chace and Tasker<sup>2</sup> in 1917, Kofoed, Kornhauser and Plate<sup>3</sup>, Maxcy<sup>4</sup>, Kennedy and Rosewarne<sup>5</sup> together with many other observers have called attention to the gastro-intestinal manifestations of infection by this parasite, which in man most often affects the duodenum. Their presence has been noted in the stomach when there is a diminution of gastric secretion. The gall bladder has likewise been the seat of their presence. *Giardia enteritis* is chronic, and the parasite has a tendency to produce considerable destruction of the intestinal mucosa. Whereas *giardia* has long been considered a nonpathological inhabitant of the bowel and its presence to the extent of 20% in school children without bowel disturbances has been reported by Maxcy, and in 6% of apparently healthy American soldiers by Kofoed and his co-workers, its universal distribution together with the manifold bowel disturbances attributed to its presence, should urge one to the possible consideration of its existence, which can readily be determined by the usual routine methods for examination.

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# Congenital Obstruction of the Urinary Tract

By N THOMAS SAXL, M D , F. A C P , New York

## I PIN HOLE MEATUS

**B**Y Pin Hole Meatus is meant a very small opening at the distal end of the urethra as it emerges from the glans penis. It is rather interesting to note that this condition seems to be more familiar to pediatricians than to those in the genito-urinary field and the probable underlying reason for this is the fact that it is frequently the cause of dysuria in the male infant. Too frequently is the diagnosis overlooked and the troublesome symptoms that it causes, are wrongfully attributed to other sources.

*Etiology* The stenosis is always restricted to the distal extremity of the urethra and rarely extends for more than one-third of an inch proximally. It is usually noticed between the second and the fourth year of life when symptoms become prominent, but has also been diagnosed in babies a few days old. We find it most difficult to account for this anomaly, and associated other congenital defects are rare. The urethra develops from two sources, the proximal part from urogenital sinus and the distal part is formed by the canalization of a plug of epithelium. An arrest of this latter process before a channel of adequate size has been formed caused congenital stenosis of the urinary meatus, but we

do not know what factors determine this irregular development.

*Signs and Symptoms* The signs and symptoms caused by this condition are two-fold. A Those due directly to interference with the outflow of urine. B Those due to the urinary infection which often follows this obstruction.

The commonest symptom is dysuria and the mother will call attention to the straining of the child at micturition, a small and intermittent flow associated with crying either caused directly by pain or by the anticipation of pain to come. In older children, we frequently notice an incontinence of urine which the mother claims is a frequency of micturition. These children are unable or unwilling to micturate until the bladder becomes distended and an overflow incontinence is established and a little urine dribbles away from time to time. This retention may even cause the bladder to distend up to the umbilicus and the retention becomes so acute that the patient may pass nothing for 24 hours. Further progress of this condition causes the overflow incontinence but the stagnation of the urine is frequently followed by infection and so pyuria will be the next symptom. In this effort to relieve the pain and obstruction the child frequently handles the penis and soon

superficial ulceration of the meatus may be noted. This ulcer frequently bleeds and so hematuria may be the first complaint. This ulcer is probably caused by some infected urine, that was retained proximal to the point of stenosis and actually massaged into the mucous membrane by the child's frequent handling of the penis.

*Diagnosis* Pin hole meatus is frequently overlooked, but it must be remembered that phimosis per se, rarely if ever, acts as an obstruction to the outflow of urine and therefore the frequency of circumcision in these cases is to be decried. The main difficulty in diagnosing congenital stenosis of the urinary meatus is the fact that the average physician forgets that such a condition exists. A simple examination will reveal the presence of a pin hole meatus but the history of the case should make one suspect its presence even before the examination is made. The complaint of dysuria including straining and dribbling during, before and after each micturition, urethral bleeding, ulcers, incontinence of urine, frequency and bed-wetting should always lead to a most careful examination of the urinary meatus, even before any other etiological factor is considered. In rare instances, if the foreskin cannot be stretched, it may even become necessary to circumcise the boy, but if such happens to be the case, it is deemed wise to warn the parents at this time that a second small operation may become necessary. When a clear view of the meatus has been obtained, it is usually not necessary to do more than look at it to decide whether stenosis is present or not because, while

one cannot define the normal size of the meatal orifice, nevertheless, a stenosed meatus is generally so like a pin hole, that the diagnosis is at once apparent. The technique by which one should examine the urinary meatus is as follows. Compress the meatus between the finger and thumb in the antero-postero direction (*i.e.*, in the line of the orifice) and this will show the real size of the opening. If the sides of the opening are apparently adherent this simple procedure will overcome this difficulty. Additional data and information may be gained by having the child urinate and watching the stream of urine for three factors. A The calibre of the stream. B Hesitancy in passing the stream. C Interruption of the act of micturition, partially from pain.

*Differential Diagnosis* Inasmuch as no other condition gives quite the same picture, the differential diagnosis should be very easy, but as mentioned above however, superficial ulcerations may give rise to bleeding. Hematuria is a common complaint in pin hole meatus, and should not be confused with hematuria from a point higher in the urinary tract. Enuresis may have various etiologies, but one should always consider pin hole meatus as a possible cause. Phimosis, as we have already noted, rarely causes an obstruction to the outflow of urine. Epispadias and hypospadias are easily recognized.

*Complications* This condition, when untreated, goes on to cause back pressure and will ultimately involve even the pelvis of the kidney. Secondary infection of the urinary tract readily occurs and in some instances hydro-



nephrosis and pyonephrosis in children may be sequences of this congenital stenosis, but up to this time there is little evidence to prove or disprove this point

*Treatment* The treatment of this condition is relatively simple. Instrumental dilatation has proven to be quite unsuccessful because of the cicatrix formation that frequently follows the same. Circumcision has in all probability been unsuccessfully performed, but if not it may become necessary to do this to allow a secondary meatotomy. The results obtained from meatotomy are eminently satisfactory and permanent.

## 2 CONGENITAL OBSTRUCTION IN THE POSTERIOR URETHRA

Congenital obstruction in the posterior urethra is among the infrequently reported anomalies. When untreated, the patient seldom attains adult life. The efficacy of urologic treatment is entirely dependent upon the early diagnosis before grave secondary changes have taken place in the urinary organs. Disturbances of urination, pyuria, hematuria, signs of nephritis, or pyelonephritis may progressively develop and should direct attention to the urinary organs and the urological examination must be made at the earliest possible moment.

*A Hypospadiophy of the Verumontanum* Bugbee and Wollstein<sup>1</sup> at the Babies' Hospital in New York City have given the most exhaustive report on this condition. Their report was based on 5,000 autopsies performed, and altogether totaled some ten cases. All of these, except one had been dis-

covered at autopsy and the ages varied from thirteen days to three and a half years. In almost every instance the usual result was kidney injury and so it would seem that surgery in these cases comes too late. One patient survived 12 years and therefore a careful urologic examination is essential in these cases as soon as the obstructive disturbance manifests itself.

*B Congenital Valvular Obstruction* Urethral obstruction due to the presence of urethral folds that we now designate as urethral valves is not a newly discovered entity. It was first mentioned by Langenbeck<sup>2</sup> in 1802 and again by Velpeau<sup>3</sup> and Guthrie<sup>4</sup> in 1832. In 1891 Eigenbrodt<sup>5</sup> is given credit for being the first to recognize this condition in the living individual. In America this condition was first described by Knox and Sprunt<sup>6</sup> in 1912 and in 1913 Young<sup>7</sup> performed the first successful operation for its correction and was also the first observer to diagnose the condition by the use of urologic instruments antepositively. Hinman<sup>8</sup> tells us that urethral valves, while they may be regarded as rare, are frequently overlooked however.

*Etiology* The location would suggest at once congenital origin. There seems to be on unanimity of opinion regarding the etiology of this condition. Bazy<sup>9</sup> in 1903 called attention to the fact that in the latter part of embryologic development, the urogenital membrane in the posterior urethra is to be found at the location of the verumontanum and inasmuch as congenital valves are almost always found in this location, some observers have assumed

that persistence of the membrane is responsible for their occurrence. Watson<sup>10</sup> believes that they appear as early as the thirteenth week and that the top of the colliculus in some way becomes attached to the roof of the urethra and it may go on for years without causing symptoms. According to Fischl's opinion a proliferation of the epithelium on the roof of the sinus urogenitalis with subsequent connective tissue adherent to the opposite wall readily accounts for the anomaly, however, none of these theories serves to explain completely all of the congenital valve formations, which have been classified by Young<sup>7</sup> into three types.

The first of these presents, on examination, a ridge on the floor of the posterior urethra, beginning at and continuous with the verumontanum and running anteriorly to divide at the bulbomembranous junction. The valve separating is attached as a thin membrane to the urethra in varying degrees about its circumference. In type two, the extension of the membranous sheets is posterior from the verumontanum toward the internal sphincter, where they are attached to the urethra. The third type is not continuous with the verumontanum, and may be found at any point in the posterior urethra. This variety presents the appearance of a diaphragm spread across the lumen of the urethra and pierced by a passage varying in size from pin-point caliber to a diameter which may convert the valve into an incomplete crescent or semicircular fold on either side of the urethra. The concavity of this diaphragm is toward the bladder which allows the valve to be flattened against the urethra by instruments passed into

the bladder but distends and produces obstruction when the urinary stream is directed against it.

Urethral valves are essentially a childhood disease. In the series of 56 reported cases by Hinman<sup>8</sup>, 12 were found in the first year of life. Fuchs<sup>12</sup> reports a case in a five-month fetus and Schmidt<sup>12</sup> another in a 7-month fetus. The oldest reported by Hinman was a man of 57 and Iveison<sup>11</sup> reported one of 85.

*Symptomatology* There is really nothing distinctive in the symptomatology of this disease. Any symptom of urinary disease such as dysuria, frequency, straining, dribbling and urgency in a very young child should make us think also of valves as a possible etiological factor. Fretfulness and restlessness usually accompanying these symptoms and persistent pyuria will undoubtedly be found. Later on evidences of back pressure with bladder distention, hydronephrosis, etc., will be noted and as a result of this an associated pyelonephritis with renal insufficiency which terminates usually in gastro-intestinal disturbances, chills, fever and eventually uremia.

*Diagnosis* With symptoms referable to the urinary tract, the diagnosis can only be made by complete urologic examination, however, physicians as a whole still present a fair amount of opposition to cystoscopy in children. This is just as easily done in a child as in an adult and there is no just cause for such an opinion. Roentgenological examination including a cystogram revealing hydroureters and hydronephrosis (which frequently accompany valve disease) is of some assist-

ance, but when the cystogram is negative a cystoscopy must be insisted upon

*Treatment* Destruction of the valves by surgical intervention or by fulguration are the only methods advisable. The results as a rule are fairly good.

*C Dislocation of the Internal Meatus* This is an exceedingly rare type of obstruction and has been reported by Day and Vivian<sup>12</sup>, in a case seen recently in Los Angeles. The obstruction in the posterior urethra is due to the fact that the prostatic urethra runs obliquely to one side and enters the bladder about 1 cm laterally to the median line. The case reported seems to be due to a malposition and overlapping of the right trigonal muscle above the left with dislocation laterally of the internal meatus and line of fusion of the two halves of the trigonal muscle. The trigone was greatly hypertrophied.

### 3 CONGENITAL URETERAL OBSTRUCTION

*A Strictures* These lesions account for more than half of all ureteral obstructions. These strictures show a very definite predilection for the ureteral extremes, i.e., the pelvic or vesical insertion. However, they may occur at any point along the course of the ureter and may be single, multiple, unilateral and bilateral. Some observers consider these obstructions as mucosal redundancies with valve formation and there is no question of doubt that this is true in many instances, however, histologic examination of these lesions reveals marked mural fibrosis.

*B Kinks* The usual site is near the ureteral pelvic junction, but may

occur at any point along the course of the ureter. Campbell<sup>13</sup> cites a case in mono-ovular twins in which autopsy revealed sharp "S" shaped kinkings in the left ureters at precisely the same point. He further mentions as a curiosity that there were also identical transduodenal bands. However, congenital kinks are exceedingly rare.

A case that illustrates congenital ureteral obstruction (see figure 1) was that of J. M., a boy of four months who was brought to the Post Graduate Hospital on December 23rd, 1929, with the complaint of fever and vomiting of about four days duration. Physical examination showed contracted pupils, reacting sluggishly to light, stiff neck, Kernig and Brudzinski. Spinal tap showed turbid fluid, 4150 cells, 91% Polys, +++ Globulin and culture later showed meningococcus. Serum treatment was instituted and continued until fluid was clear and cells down to 30. Stiff neck remained. Child did not pick up, but continued on a down-grade. Frequent taps showed no marked evidence of further pathology. About January 7th, fifteen days after admission, suspicious signs of pneumonia in the right lung appeared and the patient's temperature which had returned to normal now rose again and continued high with occasional remissions. One day later the signs of pneumonia in right chest became conclusive and x-ray showed further evidence. On January 16th, eight days later, the right chest showed signs of consolidation in upper, middle and lower lobes posteriorly and in the axilla. The patient died on January 16th, and autopsy revealed the following

- 1 Subacute fibrino-purulent meningitis
- 2 Right interstitial broncho-pneumonia with atelecasis, fibrino-purulent pleurisy and empyema
- 3 Vesicular and ulcerative infection of skin, especially neck and scalp
- 4 Punctate hemorrhages of gastric mucosa
- 5 Dilation of right heart
- 6 Acute passive congestion of abdominal viscera
- 7 Congenital aplasia of left kidney, with compensatory hypertrophy of the right
- 8 Left hydroureter and hydronephrosis

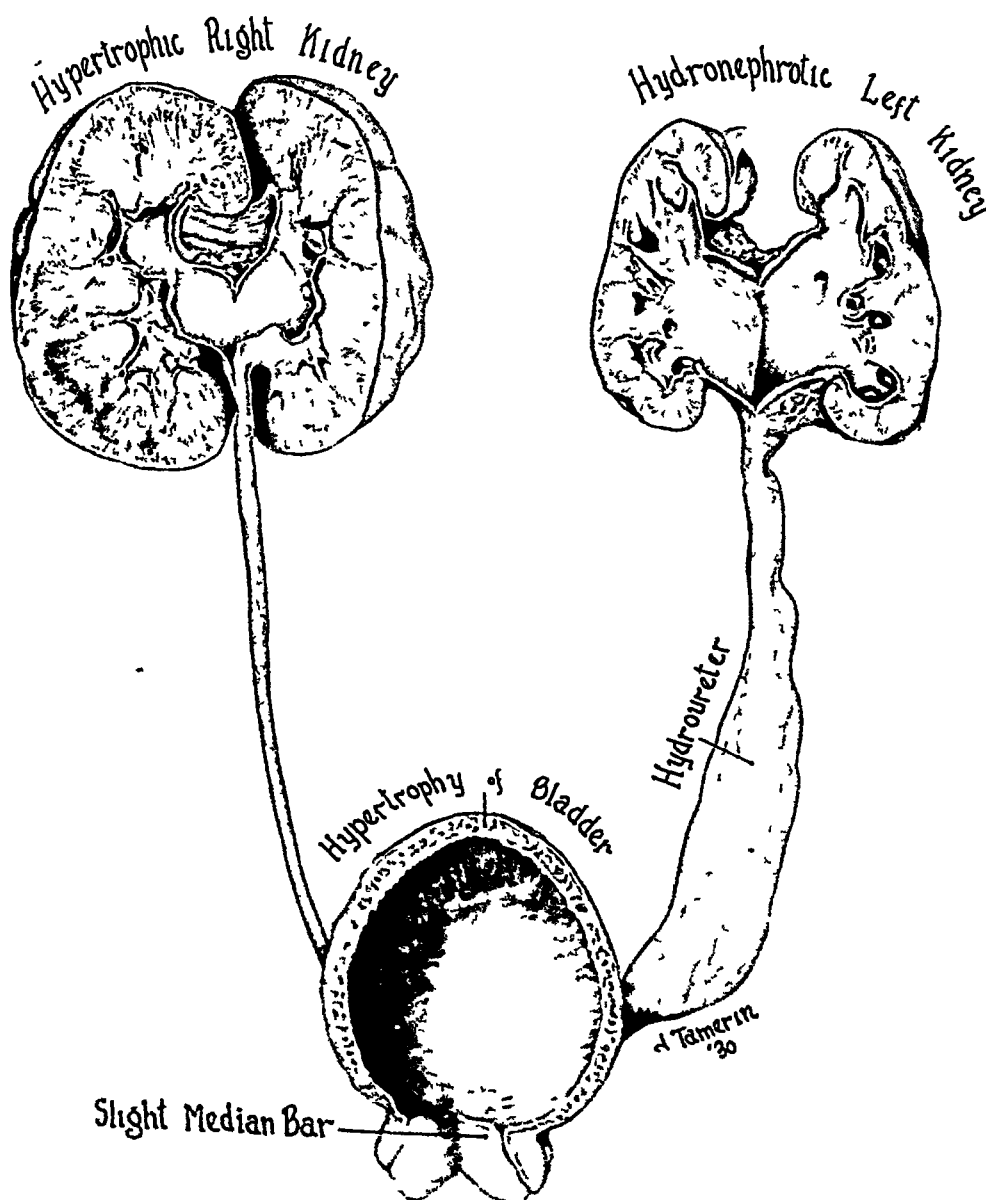


FIG 1

9 Hypertrophy of urinary bladder walls

10 Congenital vulvular stenosis of left ureteral meatus

11 Phimosis

4 *Median Bar* Some authors believe that the so-called median bar is not congenital, but is caused by chronic inflammation. Pugh<sup>15</sup> says that it is undoubtedly a sequel of an old gonorrhea. He feels that a very small percentage of our gonorrhea patients are cured and the disease remains in the deep urethra and that during the course

of years, an inflammatory condition extending from the prostate up into the vesical sphincter forms a very definite bar or ridge. These bars may simulate small median lobes or may gradually extend completely around the vesical neck forming a true collar obstruction.

On the other hand, there are those of us who feel that in addition to this type of median bar, there also exists another form which is congenital in origin as can be seen in the following case (figure II)

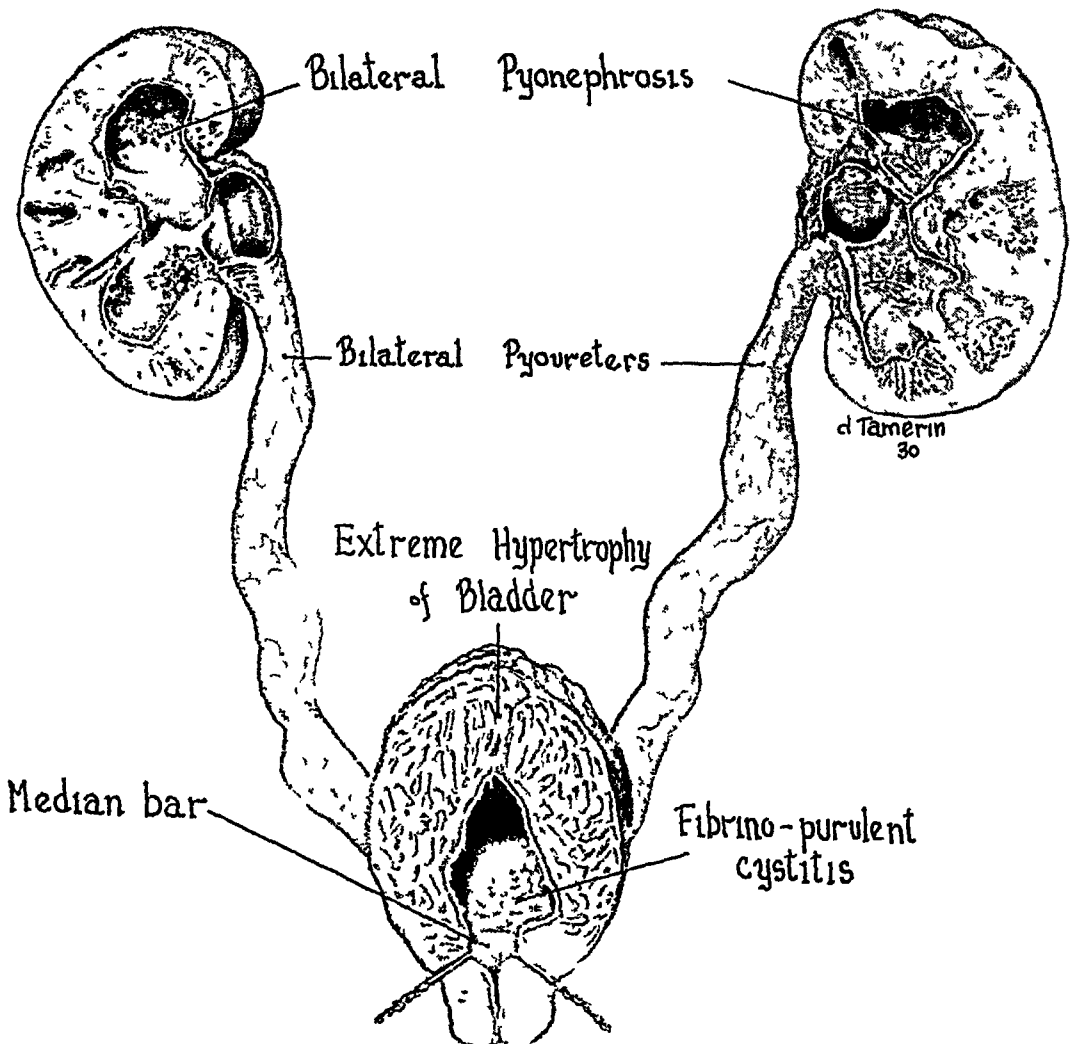


FIG 2

F N, age 15 days, admitted to the New York Post Graduate Hospital on September 12th, 1929, with a chief complaint of scrotal swelling apparently since birth. This had begun to increase in size during the 24 hours before admission so that (according to history) there had been retention of urine. This however, was not substantiated as patient voided while in hospital. The scrotal swelling increased and the penis became quite edematous. The child's general condition was more serious than the local condition would

account for. White blood cells were 34,000, the urine was loaded with pus and red blood cells. A dorsal slit was done, and a large amount of pus was obtained from scrotum. The patient died the following day. Autopsy revealed the following:

- 1 Acute pyelonephritis
- 2 Acute fibrinous peritonitis
- 3 Acute fibrinopurulent cystitis
- 4 Peri-urethral abscess
- 5 Surgical incision of scrotum
- 6 Hypertrophy of bladder
- 7 Congenital Median Bar

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# Psychiatric Consultation Service Supplied by the State Department of Health

By JAMES L. MCCARTNEY, M. D., *Chief, Division of Mental Hygiene,  
Connecticut State Department of Health, Hartford, Conn*

**A**T present thirty-eight states in the Union have some form of Mental Hygiene and Psychiatric Consultation Service. In these states there are eight hundred and fifty mental hygiene clinics,<sup>1</sup> dealing with neuro-psychiatric problems of the adult and child. Most of these organizations are privately endowed, there being only ten states which furnish these facilities through the State Department. Only one of these ten states definitely ties up psychiatry with the general health problem, this state being Connecticut, which has mental hygiene as an intrinsic part of the State health program.

Preventive medicine has become an established fact. It is now more than thirty years since the prevention of tuberculosis has become an important link in the chain of protective services, designed to control disease. At present there are about six hundred clinics for tuberculosis in operation in the United States and this number seems adequate. There are some eight hundred venereal disease clinics supplying the need in that field reasonably well.<sup>2</sup> Yet, it is evident that the eight hundred and fifty neuropsychiatric clinics mentioned are quite definitely insufficient for more than a small fraction of the need in our present social system.

The First International Congress held in Washington this last May brought out the fact clearly that mental hygiene is of paramount importance in any general health program. This need is realized when it is found that there are more patients in mental hospitals than there are physically-sick patients in the general hospitals of the whole country, and the mental hospitals are at all times so overcrowded that many needy cases are denied admission. The preventive angle of this problem is significant since at least half of all cases of mental and nervous disorders can be prevented by the timely application, largely in childhood and adolescence, of available knowledge. Every general physician is faced with the problem of handling these neuropsychiatric cases but he usually finds himself without the necessary knowledge to give the adequate treatment.

When a full-time Division of Mental Hygiene of the Connecticut State Department of Health was established, it was found that there was a need and a demand for a Consultation Service in Mental Hygiene and Psychiatry, which might be available to physicians and social agencies, who were frequently faced with personality

problems Unfortunately, there is an inadequate supply of private psychiatrists to handle these cases, and few of these psychiatrists maintain a clinical set-up Consequently, this service was made available and is furnished gratis to all recognized physicians in the State as well as to all organizations working in co-operation with such physicians All nervous and mental problems may be referred for diagnosis and advice as to treatment Persons of both sexes and all ages are examined, and although no treatment is given, whenever possible, a detailed outline of treatment is sent back to the referring party, and the patient advised to follow his advice

During a period of seven months (October 1929 to May 1930) two hundred and twenty-six cases were referred to the Division of Mental Hygiene for examination, and of this number 52 per cent were boys under eighteen, 23 5 per cent were girls, 11 5 per cent were men and 13 per cent women Of the total number referred 17 per cent were directly from physicians, 63 per cent from visiting nurses and school nurses, 7 per cent from

State agencies, and 13 per cent from private social agencies

When consultation is desired the accompanying form is filled out and returned to the central office at least two weeks before the time set for consideration, and in only emergency cases is this rule departed from This period of two weeks allows time to make a careful, social study of the patient's background and environment, which is very necessary for an intelligent examination of the patient

In making a psychiatric examination, it is necessary to study the individual as a whole Fortunately, practitioners are more and more realizing the necessity of considering all types of patients in this light In attempting to interpret deviations of character this is obviously important, for in studying behavior many persons may be involved Parents have to be reckoned with in studying their children, teachers in their pupils, and employers in their workers

In order to study the patient as a whole a four-fold examination should be made and every consultation service handling neuropsychiatric cases should

# REFERENCE BLANK

(Fill in by typewriter or printing)

NAME	DATE OF BIRTH		
ADDRESS	PLACE OF BIRTH		
SCHOOL GRADE OR EDUCATION	SEX	COLOR	RELIGION
OCCUPATION			
REFERRED BY	ORGANIZATION OR ADDRESS		
PARENTS	ADDRESS AND OCCUPATION		
(Name and Age)	FATHER		
	MOTHER	ADDRESS AND OCCUPATION	
BROTHERS AND SISTERS (In order with addresses)			
REASONS FOR REFERENCE			
INTERESTED PERSONS AND AGENCIES			
PHYSICAL CONDITION			
REMARKS			



have the standard mental hygiene set-up composed of a psychiatrist, who, of course, is a physician to begin with, and who should be well versed in general diagnoses; a psychologist, who has been trained in the testing of intelligence, and a psychiatric social worker who has had a thorough training in case history taking. It has usually been found that for every psychiatrist, a half-time psychologist, and two or three psychiatric social workers are necessary to conduct a full-time program.

To obtain an adequate idea of the patient's background, the psychiatric social worker should trace the development of his habits, particularly if they are abnormal, and the companions he selects should be ascertained, to see if there is any apparent ill effect they may have upon him. It is also necessary to know how he uses his spare time, what recreation he chooses, his interests, and where they take him. The stages by which his misconduct has grown, its early beginning, and the facts surrounding them, are important in outlining treatment. His mental accomplishments have to be accurately evaluated and a full school history which portrays both his failures and his successes must be obtained. His past ill-health may be a factor, and this must be investigated. It is also very necessary to know the circumstances of the child's conception and birth. In other words, a well-trained worker will trace in detail the development of the patient's personality. Commencing with his hereditary predisposition, she will follow step by step all the important factors until a well balanced picture is drawn. This of course nec-

essitates a detailed family history, and all this hereditary data should be gathered with insight. "Her story should give the information as to how his ancestors dealt with their life situations—whether they were able to meet reality or whether they were 'routed and fled',—whether grandfather could face the responsibilities of an ever increasing family or whether he 'deserted the ranks', cutting himself off from the family, perhaps hiding behind an effective barrier of irritability or anger, or 'buried his head in the sand' by imbibing alcohol too freely".

Scientific work of the last few years has demonstrated with new thoughtfulness that mind and body are inseparably joined together,—that abnormal mental states affect physical health, and abnormal physical states affect mental health. The mind is the correlator of all the various functions and processes of the body. If the examiner is to have a well-rounded idea of the patient's problem, he must know of his physical health. Every resource of modern medicine should be considered in the examination of the patient, for it is seldom that some form of medical care is not necessary in the treatment of these patients, often times these points being missed by the general physician, although important and significant in the consideration of the total personality. It is important to ascertain whether it is eyestrain, malnutrition, flat feet, or other defect that is producing the increasing irritability, and obviously the trouble must be corrected if the patient's behavior is to be improved. Marked feelings of inferiority nearly always accompany physical defect, and personality diffi-

culties often result from abnormal functioning of the ductless glands. Not infrequently an apparently reckless, hyper-active, troublesome person will prove to be a seriously fatigued individual whose fatigue has become a chronic state. He is too uneasy to keep still, continually "on the go" and he may try to relieve his discomfort by seeking excitement. Some of the so-called bad boys will prove to be early cases of tuberculosis. In all of the cases of speech difficulty frequently referred for psychiatric consultation, it would be absurd to try to make a diagnosis without a complete physical examination. It is thus evident why the Health Officer or the family physician is asked to make a detailed physical examination, and to send in their report previous to the psychiatric examination, and if possible, at the time of reference. Where it appears necessary, an X-ray, serological or basal metabolism test may be requested.

A well-trained psychologist can give valuable information concerning a person's ability and thus in the consideration of many juvenile problems, it is necessary to have a thorough psychological and educational examination given as routine. The patient is first given a test to determine the quantity of his intelligence, the result of these tests being expressed in terms of mental age. If, for example, his score shows a mental age of 12 years, it means that he has the same quantity of intelligence as the average child of 12 years. When his mental age is compared with his actual life age, some idea is gained of the comparative quantity of his intelligence compared with other children of the same life age.

This comparative quantity is generally expressed in terms of percentage and is called the child's Intelligence Quotient, or his "I Q". Generally speaking, children with an "I Q" of from 90 to 110 are considered to have a normal quantity of intelligence, while those below these figures are sub-normal, and those above are superior. The "I Q" should never be interpreted without an adequate social history, a complete physical examination and a thorough psychiatric examination. Emotional factors may enter into the result of an individual test so that gross injustice and real harm may be done.

In addition to the intelligence test, the clinical psychologist should give a performance test, which is important, especially in dealing with the question of vocational guidance. If possible, the child should also be given an educational test. The test of intelligence shows the child's native or potential ability but the educational test shows to what purpose he has used these abilities. The result indicates what he has accomplished. His abilities and accomplishments can now be compared. This comparison is again expressed, in terms of percentage and is called the accomplishment ratio. In this manner, at times, a dull child is found to have made better use of his intelligence than some very superior children, and thus may give insight into some of his other traits or tendencies.

In the social history, it is important to ascertain what the persons in the patient's environment think of him, in the medical examination, what the physician thinks of his body, and it is important to know what the psychologist has discovered about his

mental equipment, but it is the problem of the psychiatrist, to ascertain what the person thinks about himself, how he feels towards those in his environment, what he thinks of the world and life in general, his parents, his marriage partner, his home, his brother and sisters, and his conduct towards them. If he has been an unwanted child, how much more critical would his parents have been towards him, his simple childlike mischievousness being interpreted as innate perversity. The psychiatrist endeavors to discover what mental twist is causing the disorder. His experience with abnormal mental states gives him the technique and insight. His study of these disordered minds throws much light on normal mental mechanisms. The psychiatrist as stated above, is primarily a physician, and it is as one who heals the sick that he views the problem child or the problem adult.

In the Consultation Service as furnished in Connecticut, after the examinations as listed above are completed, the facts are all gathered together, di-

gested, and an attempt is made to diagnose the case, and treatment is then outlined. When a case is referred for consultation, a careful study is made of the local facilities for caring for neuropsychiatric cases, the schools and institutions are visited and influential citizens are interviewed, so that these individuals may be enlightened and may be better prepared to accept the recommendations that may have to be made, which at times are rather of a radical nature. Where ever possible, the referring party is interviewed and the cases are discussed in detail, so that there may be no misunderstanding. As in the examination, the treatment of most neuropsychiatric cases does not fall on one person, but included the patient, his parents, his associates, his teachers, employers and the clinician who referred the case, all of whose attitudes, many times, need changing. This may be the most important part of the treatment.

Of the 226 cases seen in consultation as before mentioned, the diagnoses were as follows

	No of cases	Percentage
Psychoses	11	5 0
Psychoneuroses	20	9 0
Neurological problems	38	17 0
Emotional problems primarily on a physical basis	23	10 2
Habit disorders	11	5 0
Personality difficulties	15	6 6
Behavior problems, not referred through courts dependent on		
Mental Defect	8	3 5
Mental Superiority	2	0 8
Environmental handicaps	38	17 0
Emotional instability	14	6 2
Other factors	6	2 6
Problems of Delinquency referred by courts, dependent on environmental handicaps	2	0 8
Intelligence Problems		
Superior Intelligence	6	2 6
Borderline Intelligence	9	3 8
Feeble-mindedness	23	10 2

This Consultation Service in Connecticut has been carried on as only one of the numerous duties of the Division, so that the time available has necessarily been limited and it has been found that the demand has been far beyond our facilities. A social examination of a case involves at least two hours of a social worker's time, many times requiring as much as half a day, while a psychiatric examination, in most cases, has required at least an hour. Although we have found many cases in which we have felt that it would have been advisable to have spent even more time than this, the demands on our service have been such that many times we have cut down our time scheduled for certain cases to less than an hour.

It will be concluded from what has been said before that in psychiatric consultation work, possibly more so, than in any branch of diagnoses, a "snap" diagnosis cannot be made, as

no two people are alike, and so no two cases are alike. Each case has its own individual causative and associative factors, so generalizations are almost impossible and extremely dangerous. It is seldom that factors needing correction are not found in all four fields listed above,—social, physical, psychological and psychiatric. Anything less than a complete study is very risky and may prove fearfully damaging. Each individual under examination must be considered a personality, if he is to be guided and helped to an adjustment of his emotions.

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# Experimental Studies of Nerve Impulses\*

## An Attempted Correlation Between Physiology and Symptomatology

By HIRAM BYRD, M. D.

*In Collaboration with*

WALLACE BYRD, A. B.,

*Detroit, Michigan*

THE list of independent observers who have recorded the arrest of remote dysfunctions by the interception of nerve impulses passing the sphenopalatine ganglion<sup>1, 2</sup>, \* has become so extensive, and the number of instances so great that it may seem a threshing out of old straw to emphasize the causal relationship involved. It is the mechanism which challenges inquiry. However, analysis of the mechanism is best begun by a careful

scrutiny of the factual basis and the logical groundwork.

That these phenomena could be interpreted as due to systemic action of the drug or to psychic reaction of the patient may be dismissed without comment. Even to raise such questions would be to proclaim an unfamiliarity with the field of observation—they are too easily answered by simple tests.

As early as 1908 Ewing<sup>3</sup> arrested eye pain (glaucoma) by anesthetization of the sphenopalatine ganglion. The observation that such arrest of pain is not accompanied by any detectable anesthesia of the eye has since been corroborated by other observers<sup>1</sup> and has been well demonstrated in traumatic ulcer of the cornea, the exquisite pain of which may be arrested while the injured cornea remains as sensitive to the touch of a wisp of cotton as its fellow of the opposite side. Moreover it has been shown<sup>1</sup> that if the arrest of pain obtained by anesthetization of the sphenopalatine ganglion resulted from the interception of the *pain message* then whenever the ganglion is anesthetized all the major regions of the body (where

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\*From the Jefferson Clinic and Diagnostic Hospital, Detroit, Michigan.

\*It should be noted that no dysfunction has been found, all cases of which are arrestible by this procedure. Although it has not yet been possible to subject to statistical analysis the proportion of cases thus relievable through the list of some seventy dysfunctions now recorded, it may nevertheless be observed that this ratio is quite variable in one dysfunction as compared with another. For example, in lumbago an ample majority of cases are relieved, and in most of these cases the relief lasts indefinitely, while in sciatica and many other dysfunctions only a minority of cases respond—perhaps a fourth or a fifth, and in these the relief is a little less likely to be permanent. Since some cases of so many maladies are relievable, however, the procedure is one of large therapeutic value.

dysfunctions may potentially be relieved) would be involved in a widespread anesthesia, and when the ganglion is injected with alcohol this anesthesia would persist for several months, which is not found to be the case at all

Also it is observed that anesthetization of the sphenopalatine ganglion may arrest dysfunctions of other categories than sensory, as motor, secretory, respiratory, circulatory and endocrine, and that a single anesthetization may arrest both sensory and motor, or sensory and secretory, or motor and secretory dysfunctions, and so on in varying combinations. Findings of this kind seem to demand that the phenomena be accorded a unity of interpretation, and that an explanation that is not equally tenable for the whole aggregate be not accepted

The demand for such an explanation suggests that we turn to physiology. Our own endeavors to obtain a physiologic explanation of these phenomena have been continued over a number of years. Among those consulted in this country and abroad was Howell, of Johns-Hopkins, who said "There is nothing known in anatomy and physiology that provides a rational basis of interpretation for the results that you claim"

If the fact that asthma, chorea or diarrhea may be arrested in certain cases by anesthetizing the sphenopalatine ganglion is at variance with the present day teachings of physiology, the variance cannot but require some modification of our physiological conceptions, since in science the observed facts make up the environment to which theories must adapt themselves

if they are to survive. The object of this paper is to suggest that the variance may be more apparent than real, and that through correlation of physiologic principles already at our disposal, it may, perhaps, disappear

#### NERVE IMPULSES\* AN ESSENTIAL FACTOR IN CAUSATION OF SYMPTOMS

It is observed that the arrest of dysfunctions may be effected through anesthetization of the strategic sphenopalatine ganglion (right or left as the case may be) (a) by topical application of cocaine or butyn, (b) by the injection of alcohol into the ganglion, or (c) by the injection of novocain into its immediate environs. From this it is concluded that the arrest of the symptom *is effected by virtue of some action that these four procedures have in common*. It cannot be anesthetization of the nerve, for alcohol does not anesthetize the nerve but destroys its fibers, nor can it be destruction of the nerve fibers, for cocaine and butyn do not destroy the fibers. They all, however, have one effect in common, namely, *to prevent the passage of nerve impulses over the treated section*. It is therefore concluded THAT NERVE IMPULSES ARE AN ESSENTIAL FACTOR IN THE CAUSATION OF THE SYMPTOMS THUS ARRESTED

#### ARREST OF DYSPNEA BY INTERRUPTING IMPULSES ON VIDIAN NERVE

In the foregoing clinical investigations, 1, 2, the dysfunction could

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\*The term *impulse* is used instead of *current*, not because it more accurately represents our conception of the entity, but out of deference to the language of physiology.

be made the subject of experimental inquiry only after it had occurred spontaneously in a state of nature. By the manner in which it was arrestible we might infer its causation, but we never directly caused it. In the following the dysfunction was not merely arrested at will, but precipitated at will as well. The experiments to be presented as illustrative of this group are based upon the relationship between nerve impulses and asthmatic dyspnea \*

Experiment 1, May 8. (Case of Mrs M, for 17 years a sufferer from paroxysmal dyspnea) During an attack of paroxysmal dyspnea the right sphenopalatine ganglion was anesthetized \* The dyspnea ceased completely within less than five minutes

\*Although the diagnosis of asthma made by the various physicians through whose hands these patients have passed seems to be correct, inasmuch as this is a study of nerve impulses rather than of symptomatology, our concern being not with the nature of the symptom but with the consistency of its reaction to our tests, the more general designation, *dyspnea*, has been chosen

While more than a hundred cases of dyspnea have been tested by anesthetization of the sphenopalatine ganglion during the attack, in only twenty-four of them has the attack been arrested. It is significant that of these twenty-four, not one has been relieved by anesthetizing the sphenopalatine ganglion of the left side—all were from the right

\*Technic of anesthetization Two drops of 50% butyn on a pledget of cotton previously moistened with 1/1000 adrenalin, placed against the wall of the nasopharynx just posterior to the tip of the middle turbinate. This technic has been standardized, and will henceforth be designated simply as anesthetization of the sphenopalatine ganglion. For details see J Mich St. Med Soc 29:294, April, 1930

The situation would seem to be analogous to that in the laboratory experiment in which the vidian nerve is sectioned at its junction with the sphenopalatine ganglion, and the distal end stimulated \*

#### ETIOLOGY NOT ATTRIBUTABLE TO THE GANGLION

We do not wish to convey the impression that the impulses involved originate at the sphenopalatine ganglion, or indeed, that this ganglion has any part to play in the etiology of these cases. It is believed that the ganglion is not usually an etiological factor at all, but serves merely as a medium of conveyance for the actuating impulses. The following case, observed in 1926, and a number of similar ones that could be cited, tend to discredit the supposition that the ganglion itself is an etiological factor

Miss J B, age 30, had been a sufferer from asthmatic dyspnea for a

\*Nearly two years ago the writer, visiting the physiologic laboratories of one of the great institutions of the middle West, witnessed the following experiment. Where the sphenopalatine ganglion and the vidian nerve in an animal had been exposed, a stimulus was being alternately applied to the vidian nerve and withdrawn. When the stimulus was applied, the respiration, heart action and blood pressure became quite disturbed, when withdrawn, these disturbances would subside. We are here reminded that the capacity of nerve impulses to cause dysfunctions is continually employed in the conduct of experiments in the physiologic laboratories. Physiologic research, indeed, would be greatly handicapped without it. An anomaly is that this fundamental physiologic principle seems never to have been correlated with symptomatology, or to have been applied, to any appreciable extent, in the practice of medicine

number of years, when it was found that anesthetizing the right sphenopalatine ganglion in mid-attack gave prompt and complete, though temporary, relief. This test was repeated on many occasions over a period of three months, always with uniform results. At length the right sphenopalatine ganglion was injected with alcohol, whereupon the dyspnea ceased. The patient continued free from the affection for six weeks, at the end of which time the dyspnea suddenly returned with all its former severity.

This raised the question whether the injection had been faultily placed, in consequence of which its effects were prematurely gone, or whether some other factor had intervened. It was expected that if the return of the symptoms were due to faulty and short-lived injection, then anesthetization of the ganglion would again relieve the dyspnea, as it had before. In such tests, however, it was found that anesthetization of the ganglion now would not relieve the dyspnea in the slightest.

**Conclusion.** The alcohol injection was still in effect, and the sphenopalatine ganglion was now not even playing a passive role in the etiology of the dyspnea, otherwise its anesthetization would have arrested the symptoms. It would seem that when the ganglion was injected with alcohol, the nerve impulses actuating the dyspnea were more or less permanently intercepted, and that for a time this prevented the recurrence of the malady. But at the end of six weeks, while the ganglion was still impervious to the passage of impulses, *some change supervened*, resulting in the return of

the symptoms in spite of this obstruction.

The question now arises, what was this sudden change, permitting the dyspnea, formerly arrested at the ganglion, to return with the ganglion still blocked? Was it simply the routing of the actuating impulses that had changed—a detouring of the obstructed ganglion? Apropos, that nerve impulses do have alternative routings to which they may be diverted according to the resistance encountered, we have no less authority than that of Ranson<sup>4</sup>.

The thought that there may be a considerable diversity of routing of nerve impulses is a very fruitful one. It would account as well for the numerous cases in which the dysfunction is not arrestible at the sphenopalatine ganglion at all, as for cases like the preceding, in which the ganglion, after a time, ceases to be strategic.

#### RELEVANT PRINCIPLES OF ANATOMY AND PHYSIOLOGY

Although our experiments have indicated that nerve impulses are capable of causing dysfunctions, and although in certain cases studied we find evidence of these impulses moving over the vidian nerve in a direction away from the sphenopalatine ganglion, still it is to the fundamental principles of anatomy and physiology that we must turn for a larger conception of the factors involved. From anatomy we learn that the structural unit of the nervous system is the neuron, that is, the nerve cell with its processes. In the words of Ranson<sup>4</sup> "These cellular units remain anatomi-



cally separate, i e., while they come into contact with each other at the synapses, there is no continuity of their substance" From physiology we learn that whatever the nerves do, they do by means of impulses or currents sent along their course It is these impulses that make the muscles contract, the glands secrete, the heart beat faster or not so fast, that convey messages, as of sensation, pain, emotion, thought—in fine, it is by means of these impulses that we live and move and have our being

Learning from physiology that the active constituent of the nervous mechanism is the impulse, without which the organism could not maintain its functions, simplifies our thought processes Visualizing the nerve impulse as being passed from neuron to neuron, as a ball is passed across the field from player to player, we are relieved of the necessity of thinking in terms of a complex "wiring system" and may think in terms of the impulses moving over that system No less clarifying to our thought processes is the conception, well expressed by Ranson, that nerve impulses have a variety of alternative routes which are taken according to the resistance encountered.

Physiology offers us even further help, however, for we are taught by Howell<sup>7</sup> that efferent impulses flow out from the brain "in a more or less continuous stream" to "motivate and stabilize" the various physiologic functions while from Sir Arthur Lovatt Evans<sup>8</sup> we learn that the transition from function to dysfunction is quantitative "A state of disease is never a thing in itself, but is always a quan-

titative change in some physiological process, an increase or diminution of something that was there to begin with."

Reflection on these basic principles can hardly fail to bring us to the conclusion that efferent impulses must not always be distributed in the right quantum, since every mechanism is subject to imperfections, and that efferent impulses distributed in sufficiently abnormal quantum must result in dysfunction For example, in an eye with poor drainage, efferent impulses reaching the ciliary body and iris in excess might over-motivate the intraocular secretions as to cause a rise in intraocular tension, thus producing the dysfunction we know as glaucoma Similarly efferent impulses in excess reaching the musculature of the arterioles might unduly contract them, producing, if the contraction was general, hypertension, or if local, Buerger's disease or Raynaud's disease<sup>7</sup> Reaching other muscles, such excess impulses might produce cramps or spasms, as spasm of the esophagus, observed by Sluder,<sup>8</sup> or bronchiospasm, or asthma<sup>1,9</sup> Upon reaching the motor terminals of a striated muscle, such excess impulses, if more or less continuous, would be expected to produce spastic paralysis,<sup>10</sup> or if intermittent and incoordinated, chorea<sup>11</sup> In the secretory glands of the intestine they would be expected to produce diarrhea,<sup>8</sup> in the thyroid, hyperthyroidism<sup>1</sup>

#### CONCLUSIONS

I The arrest of dysfunctions by anesthetization of the sphenopalatine ganglion is not to be interpreted as the

result of any systematic action of drugs or psychic reaction of the patients

2 The perception of pain might be arrested by interference with either the *cause* or the report to the center of consciousness—the pain message. It is demonstrable that our results are not achieved by intercepting the *pain message* (a) because anesthesia is not detectable in the erstwhile locus of distress, (b) because the widespread anesthesia involving head, neck, trunk and extremities which such an interpretation would postulate whenever the ganglion is anesthetized is not found to exist, and (c) because not merely subjective but *objective* dysfunctions, such as dyspnea, chorea, diarrhea and hypertension may be arrested by anesthetization of the sphenopalatine ganglion

Experiment 2, May 12 In the same case  $\frac{1}{2}$  cc 1½% novocain was injected into the right sphenoid sinus. The dyspnea was again arrested within less than five minutes

Experiment 3, May 27 With a 10 cm needle, slightly curved at the tip,  $\frac{1}{2}$  cc 1½% novocain was injected as

far back and as far lateral as possible beneath the sphenoid sinus, near the path of the vidian nerve. Again the dyspnea was immediately arrested in mid-attack

Up to the present time (July 10) the dyspnea has continued to be arrestible in mid-attack at any one of these three points, as follows. By anesthetization of the right sphenopalatine ganglion, by injection of anesthetic solutions into the right sphenoid sinus, and by injection or topical application of anesthetic solutions beneath the sphenoid sinus along the path of the vidian nerve

Conclusion Confirming Sluder's observations, made as far back as 1912, that anesthetic solutions may act through the bony tissues of the vidian canal, these experiments demonstrate the arrest of dyspnea by the interception of nerve impulses passing over the vidian nerve (a) at its extremity in the sphenopalatine ganglion (point 3 in figure,) and (b and c) at points along its course through the floor of the sphenoid sinus (points 4 and 6 in figure)

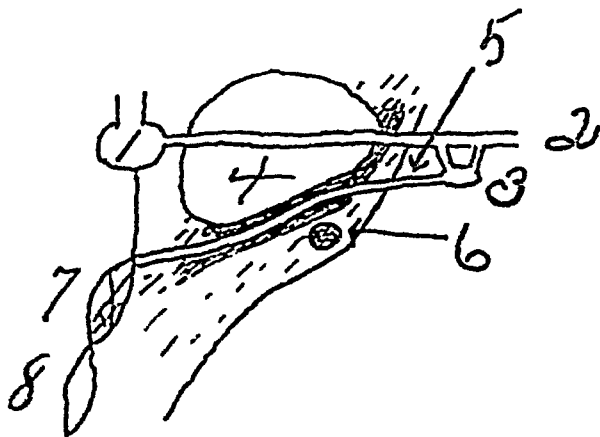


FIG 1

### CAUSING DYSPNEA AT WILL DIRECTION OF IMPULSES

While the above experiments indicate that the passage of impulses over the vidian nerve was an essential factor in the causation of the dyspnea, they do not give us the direction in which such impulses were moving—a point on which the following experiment may perhaps throw some illumination

Experiment 4, May 23 (Case of J. G., for 15 years a sufferer from paroxysmal dyspnea) The patient came in free from dyspnea, but a mild faradic current applied to the sub-sphenoid region (point 6 in figure) brought on an attack, which continued after the stimulus was withdrawn. The right sphenopalatine ganglion was now anesthetized, whereupon the attack was immediately arrested. After this had been done it was found that faradic stimulation of the vidian nerve would still bring on the symptoms, but they would subside promptly as soon as the stimulation ceased

Experiment 5, May 30 In the same case it was found that stimulation of the sphenopalatine ganglion would bring on the dyspnea when the vidian pathway was open, but would not after the vidian nerve had been blocked. That the stimulus was actually reaching the sphenopalatine ganglion was indicated by the paresthesias obtained in the sphenopalatine distribution

Conclusion These tests would seem to indicate that the impulses producing the dyspnea were passing over the vidian nerve in a direction away from the sphenopalatine ganglion in-

stead of toward it, as some have supposed

3. The fact that the arrest of dysfunctions may be effected by the use of cocain, butyn, novocain, or alcohol indicates that it results from the one property which these four have in common the interception of the passage of nerve impulses. *In other words, nerve impulses are an essential factor in the causation of these dysfunctions*

4 That nerve impulses are capable of causing dysfunctions, it is noted, is a principle continually employed in the physiologic laboratory as an incident to numerous experiments

5 Our own experiments with nerve impulses, by which we not merely arrest a dysfunction at will, but provoked it at will also, give further evidence that nerve impulses may cause dysfunctions

6 That we have been able to provoke dyspnea by applying a stimulus to the vidian nerve while its terminus at the sphenopalatine ganglion was blocked indicates that the direction of these impulses over the vidian is not toward the sphenopalatine ganglion, but the opposite toward the carotid plexus

7 From the correlation of two fundamental principles of physiology (the principle that the organism is motivated by efferent impulses and the principle that the transition from function to dysfunction is quantitative) we are led to the conclusion that efferent impulses are expected to be sometimes distributed in abnormal quantum, dys-stabilizing functions and converting them into dysfunctions

## COMMENT

Perhaps the *nerve impulses* of the clinic, the *efferent impulses* of physiology, and the *electric energy* of the bipolar theory may ultimately be identified as a single entity.

The bipolar theory, which postulates that the nerves serve, not merely for the transmission of messages but for the distribution of energy, and the findings of the clinic are strikingly in accord. Evidence that the nerve currents investigated in the clinic not only motivate and dysmotivate functions,

but are *capable of traumatizing the cells themselves*, is reserved for treatment in a subsequent paper. For the present it is sufficient to show that these currents, which are capable of *causing pain, are not pain messages*. The fact that these currents actuate motor, secretory, and other energy manifestations suggests that their study may not only bring about a correlation between symptomatology and physiology, but may integrate the work of the clinic with that cosmic energy conception of living processes, the bipolar theory.

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# A Comparison of the Diagnostic Value of the Wassermann, Kahn and Micro-Precipitation Tests for Syphilis\*

By NORBERT ENZER, M D,\*\* Mrs G V HALLMAN, M Sc, ELEANOR A. CONWAY, B A, and LOIS HYSLOP, B A, Milwaukee Wis.

THE diagnosis of syphilis by serological methods has become universal. Indeed, the tendency on the part of clinicians is to rely solely, or almost so, on the findings of the serologist. In hospital practice it is becoming common to have a serological test performed routinely on all patients. In our experience this is excellent practice, and a good axiom for adoption would be "a reliable serological test for syphilis should be performed on every new patient." In a large percentage of instances the clinical discovery of a previous syphilitic infection is well-nigh impossible, and a thoroughly reliable test will uncover many such cases. We do not advocate that the results of the test be used as the sole criterion of treatment, but the test or tests may be used as a reliable diagnostic procedure. In any event the results of the test should stimulate the clinician to search for corroborative findings by physical examination and through the medium of a carefully taken history. In view of the difficulties obstructing the clinical detection

of syphilis, and also in view of the large number of patients being treated for conditions in which a careful inquiry for a syphilitic infection is not made, as, for example, in accidents, surgical conditions and a variety of infections, a test which will disclose the presence of a syphilitic infection is of prime importance. Whether or not the syphilis so discovered bears any relation to the complaints of the patient is, of course, a matter for the attending physician to decide. Since the adoption of routine Wassermann and precipitation tests in this hospital there have been discovered many latent and old cases of syphilis, the presence of which was entirely unsuspected by the physician. The value of such discoveries has, of course, been of inestimable value to surgeons and physicians alike, and we feel has aided in clearing up many puzzling and obscure clinical syndromes and complications.

Such tests must have a very high degree of accuracy. The discovery of syphilis will increase as the sensitivity of the tests increase. With this in mind we performed Wassermann, Kahn and two micro-precipitation tests

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\*From the Laboratories of Mount Sinai Hospital, Milwaukee, Wis.

\*\*Director of Laboratories.

One of the latter called for Kahn's antigen and is conveniently labelled in this paper the Micro Kahn test, the other is the micro-precipitation test of Kline, called here the Kline test. The use of the term Micro Kahn is solely for convenience and does not imply any relationship to the standard Kahn test. The only thing common to both tests is the use of the same antigen. These tests were performed on several groups of sera and the results of the tests compared with each other and with the clinical data obtained from the attending physician in all of those cases giving a positive reaction in any one test and in any degree.

In the first four series the Wassermann technique called for two antigens. One of these was a cholesterinized alcoholic extract of dried beef heart made in the laboratory, and the other was Kolmer's cholesterinized lecithinized alcoholic extract of heart muscle, and was obtained from Dr Kolmer's laboratory. In the fifth series a third antigen was added, namely, the antigen obtained from Dr Kline, the same as was used in his micro-precipitation test. We found Kline's antigen thoroughly reliable and satisfactory. The Wassermann technique included a primary incubation of complement and antigen in an ice-water bath at 6° to 8° C. Final readings were made after incubation of the system in a water-bath at 37° for 15 minutes. Fresh sheep cells and fresh pooled guinea pig complement were obtained each day for most of the tests. Complement and amboceptor were titrated daily. Antigen controls were set up with each group of sera, as well as known + plus and negative

sera. Amboceptor was standardized against a 1:10 dilution of complement and 0.5 c.c. of 5% sheep cells. The greatest dilution of amboceptor which gave complete hemolysis after 15 minutes incubation in a water-bath at 37° C was used as the standard. All sera were inactivated for 20 minutes at 56° C for the Wassermann and precipitation tests.

For the Kahn test we used the antigen supplied by the Michigan State Board of Health and followed the technique laid down by Dr Kahn.<sup>1</sup> Readings were made after 15 minutes' incubation in a water-bath at 37° C. The micro-precipitation test with Kahn's antigen was performed according to the technique described by Kline and Young,<sup>2</sup> and read after 10 minutes' incubation at 37° C. Kline's micro-precipitation test was performed according to the technique described by Kline and Young,<sup>3</sup> and employed the very sensitive emulsion of an antigen obtained from Dr Kline. These were not incubated, but were read after 3 minutes rotation of the slides.

There are three points of view from which the results of these studies may be compared. They may be compared from the standpoint of relative agreement with each other, of absolute agreement with each other, and, thirdly, their agreement with the clinical findings and hence their relative sensitivity.

Accepting a difference of negative to 1 plus or more and 1 plus to 3 plus or more as disagreements gives an index of comparative value and demonstrates the percentage of relative agreement. Such an analysis cannot be considered indicative of the true

sensitivity of the tests, but may be considered as an index of practical value to the clinician, and as reasonably accurate. Thus, in Table I, Part A, 319 specimens were examined by a two-antigen Wassermann and the Kahn tests. The percentage of agreement was 99.06%. In Part B of the same table is given the result of the same Wassermann test with the Kahn and Micro Kahn tests performed on 635 specimens. There was a total agreement of 96.7% and a disagreement of 0.629% between the Wassermann and Kahn, 3.46% between the Wassermann and Micro Kahn, and the same difference between the Kahn and Micro Kahn. The differences occasioned by the introduction of the micro-precipitation test are of significance and will be discussed later. In Part C are the results of the Wassermann, Kline and Kahn tests performed on 1,244 specimens. A total agreement of 96.78% was obtained. In this series

the percentage of disagreement between the Wassermann and Kahn tests was 1.45%; between the Wassermann and Kline tests 2.01%; and between the Kahn and Kline tests 2.41%.

In Table II the results of these tests performed on 4,473 specimens are given. This series includes the three groups given in Table I, with in addition two groups comparing the two micro-precipitation tests with the Wassermann and one group in which the three-antigen Wassermann was employed. In this second table the disagreements are based on a difference of 1 plus in any test. Thus, a 3 plus Wassermann and a 4 plus Kahn is considered a disagreement. Hence, the figures given below record the absolute differences and are a true index of the sensitivity of the various tests. Therefore, the percentage of agreement is lower than in Table I.

Of the 4,473 specimens, 462 gave a positive reaction in at least one of the

TABLE I  
DIFFERENCES OF 0-1 PLUS OR MORE, & OF 1 PLUS-3 PLUS OR MORE CONSIDERED  
DISAGREEMENTS. COMPARISON BETWEEN WASSERMANN'S AND KAHN'S

COMPARISON BETWEEN WASSERMANN'S AND KAHN'S			
A	Total Number 319	Percentage of Agreement 99.06	
COMPARISON BETWEEN WASSERMANN'S, KAHN'S, AND MICRO KAHN'S			
B.	Total Number 635	Percentage of Agreement 96.7	Percentage of Disagreement
			Wass & Kahn . . . 0.629
			Wass & Micro Kahn . 3.46
			Kahn & Micro Kahn . 3.46
COMPARISON BETWEEN WASSERMANN'S, KLINE'S AND KAHN'S			
C.	Total Number 1,244	Percentage of Agreement 96.78	Percentage of Disagreement
			Wass & Kahn . 1.45
			Wass & Kline . . . 2.01
			Kahn & Kline . . . 2.41

tests, and as low as a 1 plus is considered a positive reaction for the purpose of this analysis. 141 of these latter were positive in the same degree in all of the tests performed, and all were syphilitic, according to information obtained from the attending physicians. 321 specimens showed differences in the degree of reaction, hence a total disagreement of 7.13%.

In the 321 disagreements, 234 were in sera from syphilitic patients, the other 87 were from nonsyphilitics and from those about whom no information could be obtained. The relative sensitivity of the various tests is shown in Table III, which is based on the disagreements recorded in Table II. In our hands, the Wassermann was slightly more sensitive than the Kahn test, the Micro Kahn more sensitive than the Kahn, and the Kline more sensitive than any of the other three

tests. Both the Micro Kahn and Kline tests, however, were positive in more nonsyphilitic sera than the Kahn or Wassermann tests. This is better shown in Tables IV and V. Table IV is a record of the disagreements in a group of known syphilitic patients, but includes only those in which a negative reaction was obtained in one test and a positive in the others. Numbers 2, 3, and 43 in this table are rechecks, but are included since a negative reaction and an anticomplementary reaction were obtained on one occasion. In this group the Kline test proved to be most sensitive in 20 of 34 tests; the Micro Kahn in 4 of 10 tests, the Wassermann in 7 of 45 tests, and the Kahn in 2 of 45 tests.

In Table V are recorded the results obtained on a group of sera from nonsyphilitic patients and those about which we had no clinical data. We

TABLE II

Number of Reactions	4,473	Reactions 4 Plus in All Tests	115			
Negative Reactions	4,011	Reactions 3 Plus in All Tests	12			
Positive Reactions	462	Reactions 2 Plus in All Tests	5			
	—	Reactions 1 Plus in All Tests	9			
Total Disagreement—7.13%		Positive Agreements (All Known Syphilitics)	141			
Number of Disagreements (Based on a Difference of 1 Plus in Any Test)			321			
(233 of These Are Known Syphilitics)						
	Wass. & Macro Kahn	Wass., Macro Kahn, & Micro Kahn	Wass., Macro Kahn, & Kline (2-Antigen Wass.)	Wass. Micro Kahn & Kline	Wass. & Kline	Wass., Macro Kahn, & Kline (3-Antigen Wass.)
Total Reactions	319	635	832	592	1184	911
Agreements	284	575	767	517	1050	858
Pos. Agreements	15	12	21	9	43	41
Disagreements	20 (17%)	48 (37%)	44 (21%)	66 (43%)	81 (58%)	62 (50%)

\*—syphilitic



must assume, for the purpose of this report, that the positive reactions were false, hence the Kline test gave a falsely positive reaction in 15 of 31 tests, the Wassermann and Kahn in 3 each of 44 tests, and the Micro Kahn in 3 of 12 tests

These tables indicate that the Kline test is more sensitive in syphilitics, but also gives more falsely positive reactions. However, in view of the experience we have had, as demonstrated

in Tables II, III, and IV, we are disposed to believe that many of these patients may be syphilitic. We therefore consider that the results of the test should not be lightly considered and passed over. Indeed, a positive reaction in any test, provided it is performed correctly, is sufficient justification for a recheck, and a persistently positive reaction must be investigated for syphilis with great care. A provocative dose of neoarsphenamine will

TABLE III  
RELATIVE SENSIBILITY OF THE VARIOUS TESTS BASED ON DISAGREEMENTS IN TABLE II

Tests	Relative Disagreements Sensitivity				Results Obtained					
	Total	Number Syphilitic	Total More Sensitive	Number Syphilitic	Wass	Macro Kahn	Micro Kahn	Kline	Total	Number Syphilitic
Wassermann and Macro Kahn	20	17	10	10						
			10	7						
Wassermann Macro Kahn and Micro Kahn	48	37	6	5	Neg	Neg	Pos		10	3
			3	3	Neg	Pos	Pos		1	0
			20	13	Pos	Pos	Neg		7	6
					Pos	Neg	Neg		1	0
Wassermann (2 antigens) Macro Kahn and Kline	44	29	7	6	Neg	Neg		Pos	10	0
			1	0	Neg	Pos		Pos	4	3
			20	8	Pos	Pos		Neg	1	1
					Pos	Neg		Neg	1	0
Wassermann Micro Kahn and Kline	66	43	20	14	Neg		Neg	Pos	7	2
			0	0	Neg		Pos	Pos	3	2
			22	12	Pos		Pos	Neg	1	0
					Pos		Neg	Neg	2	2
Wassermann and Kline	81	58	30	24	Neg			Pos	18	7
			51	37	Pos			Neg	4	0
Wassermann Macro Kahn and Kline (3-antigen Wassermann)	62	50	8	7	Neg	Neg		Pos	16	10
			0	0	Pos	Pos		Neg	2	2
			32	22	Neg	Pos		Pos	6	3
					Pos	Neg		Neg	2	1

frequently bring about a more strongly positive reaction

In this connection we find ourselves in total agreement with Kolmer,<sup>4</sup> who states, "The Wassermann, Kahn and all other serum reactions in syphilis are biologically nonspecific, they possess an extremely high degree of practical specificity under proper technical conditions. They are subject to numerous technical errors, and these are almost entirely responsible for falsely positive reactions. The serum diagnosis of syphilis is best served by employing two or more procedures as a comple-

ment-fixation and a precipitation test of proved merit. The various serum tests for syphilis are not too sensitive, but rather are not sensitive enough."

The opportunities for technical error are greater in the Wassermann test than in the precipitation tests. But the precipitation tests offer certain difficulties calling for care and experience to overcome. The lower degrees of positiveness are often difficult to estimate. In the micro-precipitation tests false readings may be obtained if the slide is not evenly and uniformly rotated. Too much emphasis cannot be

TABLE IV  
KNOWN SYPHILITICS IN WHICH A NEGATIVE REACTION WAS OBTAINED IN 1 OR MORE TESTS

No	Wassermann	Kahn	Micro Kahn	Kline	No	Wassermann	Kahn	Micro Kahn	Kline
1	0	2 plus			24	3	0		0
2	4 & 3	4 & 3	4 & 0		25	0	0		1 plus
3	4 & a c	4 & 4	4 & 4		26	2	0		3
4	4	4	0		27	2	1		0
5	4	4	0		28	1	0		2
6	4	4	0		29	0	0		2
7	0	0	1		30	0	0		2
8	0	0	2		31	0	0		3
9	2	2	0		32	2	1		0
10	neg	0	1		33	2	2		0
11	neg	0	1		34	0	1		3
12	1	2		0	35	0	2		3
13	0	0		1	36	4	2		0
14	0	0		1	37	0	0		2
15	0	3		3	38	0	0		3
16	3	0		2	39	0	2		4
17	0	1		1	40	0	1		1
18	a c	1		2	41	4	1		3
19	0	1		1	42	1	0		2
20	0	0		2	43	4 & 3	4 & 0		4 & 4
21	2	0		2	44	0	1		3
22	2	0		0	45	3	0		4
23	1	0		2					

Wassermann Most Sensitive in 7 (45 Tests)  
Kahn Most Sensitive in 2 (45 Tests)  
Micro Kahn Most Sensitive in 4 (40 Tests)  
Kline Most Sensitive in 20 (34 Tests)

placed on the care with which the emulsion of the antigen must be made in the Kline test. It is perhaps the most common source of error.

The usefulness of the Kline test perhaps has a wider application than the other precipitation tests. The readings seem to us to have been more distinct and clear cut than those obtained when Kahn's antigen was used. Further, it is not necessary to incubate, and thus evaporation is more easily controlled. The test can be performed quickly and is extremely useful as an emergency measure. It is our practice to do a Kline test on every donor at the same

time as the compatibility test is being performed. This gives an excellent control over donors for blood transfusion, and is especially reassuring when donors not on an official list and therefore not subject to test at stated intervals, are used. Nevertheless, we feel that there are always chances for technical error. In this laboratory a stand is taken against being hurried by physicians anxious for their reports. If the test or tests are valuable and worthwhile, they are worth doing well. Accuracy is far more important than speed. Yet there are occasions when the micro-precipitation test may be

TABLE V  
CLINICAL DATA UNKNOWN

No	Wass- ermann	Kahn	Micro Kahn	Kline	No	Wass- ermann	Kahn	Micro Kahn	Kline
1	0	I			23	I	0		I
2	0	I			24	0	2		3
3	I	I	0		25	I or 0	2		2
4	0	0	I		26	2	0		2
5	0 & 0	0 & 0	0 & 2		27	2	0		2
6	0	0	2		28	2			0
7	0	0	I		29	I or 0	0		I
8	0	0	2		30	I or 0	0		I
9	0	3			31	I or 0	0		I
10	0	0	I		32	I or 0	0		2
11	0 & I or 0 & 0	0 & 0	0 & I		33	0	0		I
12	I	I	0		34	0	0		I
13	0	0	I		35	0	I or 0		2
14	0	0		I	36	0 or I	0 & 0	0 & I or 0	
15	0	0		I	37	0	0		I
16	I or 0	0		I	38	0	0		2
17	0	I		0	39	0	I		2 & 3
18	0	0		I	40	0	0		2
19	0	0		2	41	0	0		3
20	0	0		I	42	0	0		I
21	0	0		2	43	0	0		2
22	0	I		2	44	0	0		2

Considering 2 Plus or Better as Positive —

Wassermann	Positive in	3 (44 tests)
Kahn	Positive in	3 (44 tests)
Micro Kahn	Positive in	3 (12 tests)
Kline	Positive in	15 (31 tests)

called for. A positive result is enough to warrant considering the individual a syphilitic until further studies can be made. The combined use of the Wassermann and a precipitation test seems to be the best method of serum diagnosis for syphilis. The Kline micro-precipitation test is easier to perform than the Kahn test, and in our hands has proved more satisfactory.

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- <sup>3</sup>KLINE, B. S., and YOUNG, A. M., A Microscopic Slide Precipitation Test for Syphilis, Jour of Lab & Clin Med, 12:477, 1927.
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# A Probable Case of Pituitary Disease Among Men of the Old Stone Age

By HARRY GAUSS, M D , Denver, Colo

MAN'S infirmities are as old as man himself, and in some instances the infirmity existed as a potential pathologic state before man's advent on this earth, awaiting his arrival to fasten itself upon him. Man being but a stage of a constantly changing cycle of biologic organisms is heir to the complexities of the struggle for existence that dominates the world. Tuberculosis for example is thought to have existed long before man made his appearance, and arriving man proving susceptible to this already existing disease became afflicted with it. Tuberculosis as a disease antedates man. Human tuberculosis is a subsequent chapter to bovine tuberculosis which follows avian tuberculosis which had its antecedents in the evolutionary history of the disease.

Elsewhere we have expressed the opinion that tuberculosis as a disease "did not arise with civilized man but rather it existed even in the most primitive prehistoric man, although without doubt the social complex of civilization may have modified some of the aspects of its pathology, epidemiology and symptomatology" that it became a disease entity when "a suitable host appeared on earth upon which the tubercle bacillus was capable of adapting itself as a parasite. It

is known that tuberculosis occurs spontaneously in mammals such as in man and cattle, in birds of which fifty-five afflicted varieties have been described, in reptiles such as snakes, in amphibians, in fish such as the carp, etc. Tuberculosis as a disease probably occurred in the Cambrian Age as a disease of fish. As the bacteria encountered the evolution of the species they successively adapted themselves to the emerging species, but this adaptation was consummated only through long periods of time." When man appeared in the Cenozoic age, tuberculosis was an old disease, it probably had already existed for some thirty million years.

Moodie places the beginning of disease at a much earlier period than this, "Disease," he states, "doubtless began with the inception of antagonism between two forms of life, and this may have occurred as early as the Archeozoic, and disease thus may be as old as life itself."

That man's infirmities are as old as man is definitely proven by the oldest records of man which is the skeletal remains of *Pithecanthropus erectus*, the ape man of Java, whose age has been estimated at a half million years. A glance at the photograph of his skeletal remains will show that old Pithe-

canthropus himself had his troubles. At the upper end of the left femur along the line of the tendinous attachment of the iliopsoas and pectineus muscles is seen a large exostosis. In all probability old man Pithecanthropus became disturbed when his leg began to swell and he lost speed in the chase and perhaps had difficulty in avoiding his natural enemies. Who knows that but for the tumor of his leg he might have gone the way of his associates and there would have been no evidence of man of this date since there have been no other skeletal remains of his associates discovered thus far. So maybe after all we are indebted to that tumor for preserving to us indirectly the oldest record of man thus far discovered. Be it as it may human pathology is as old as homo sapiens.

So if we presume to interpret a bit of evidence as an instance of pituitary disease which occurred in the Aurignacian or Late Stone Age approximately 20,000 years ago the concept is at least consistent with established principles of science.

The writer's attention was called to a photograph of a figurine in Obermaier's "Fossil Man in Spain" by J. A. Jeancon of the Smithsonian Institution, to whom the writer is indebted for being stimulated into this effort. The following description of the figurine is given by Professor Obermaier: "The Aurignacian region of western central Europe includes besides France the northern part of Spain, Belgium and England where Aurignacian industry has been found in the cave of Paviland Glamorgan-shire, on the west coast of Wales. This

region extends east of the Rhine through all central Germany where the Aurignacian is admirably represented in the cave of Wildscheurer, near Steeten on the Lahn, Rhine Province, in the caves of Sirgenstein, near Schelllingen and of Bockstein, near Langenau, in Württemberg, and in the cave of Ofnet, Bavaria. There are also many Aurignacian stations in the loess of Lower Austria in the valley of the Danube between Melk and Vienna. Mention may be made of the station of Willendorf, excavated by me in 1908, where a section of loess twenty meters thick was found to contain no less than nine archeologic strata, embracing the entire evolution of the Aurignacian industry and separating one from another by sterile strata. The fauna included the woolly mammoth (frequent) woolly rhinoceros, cave lion, lynx, wolf, fox, Arctic fox, bear, wolverine, hare, wild boar, bison, ibex, chamois, Saiga antelope (?), reindeer, stag, giant deer and horse. The upper stratum belonging to the Late Aurignacian, contained a figurine eleven centimeters in height, made of porous limestone, well preserved and with traces of pink color. It represents a nude woman with largely developed breasts and hips but no true steatopygia. The hair is arranged in concentric circles around the head; the face, on the other hand, is quite ignored. The legs and arms are very meager, being of secondary interest to the artist. The only ornament represented is a sort of bracelet indicated by coarse dots on the forearm.

With the authenticity of the figurine vouched for by Hugo Obermaier, Professor of Prehistoric Archaeology at

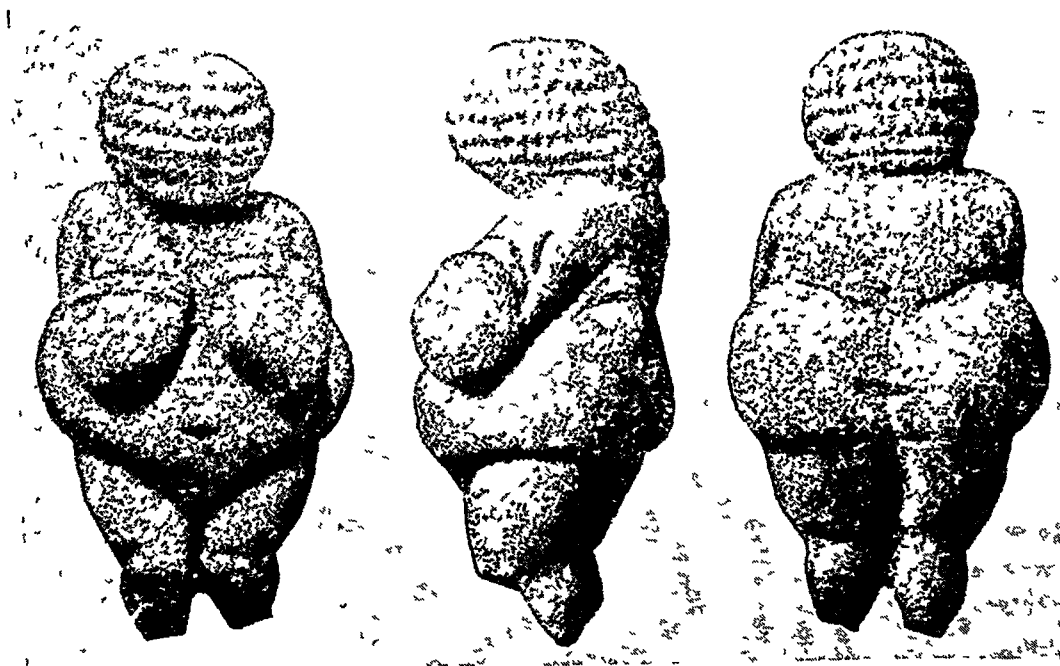


FIG 1

Figurine of an Aurignacian woman, about 20,000 years old, discovered by Professor Obermaier at Willendorf, Lower Austria, in 1908. The distribution of the excess fat in the subject is suggestive of pituitary disease. Reproduced by permission from Obermaier's "Fossil Man in Spain," courtesy of The Hispanic Society of America.



FIG 2



FIG 3

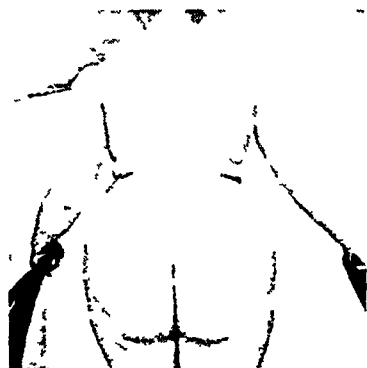


FIG 4

Some modern prototypes of the Aurignacian woman. Three cases of authenticated pituitary disease taken from Harvey Cushing's "The Pituitary Body," J. B. Lippincott Company, 1912. Reproduced by permission. The photograph on the left is Dr. Cushing's Case No. XXXV, Hypopituitarism of young adult life (dystrophia adiposo-genitalis). The middle photograph is his Case No. XXXVII, Adult Hypopituitarism with extreme corpulence and high carbohydrate metabolism. The photograph on the right is his Case No. XXXVI, Adult Advancing Hypopituitarism.

the University of Madrid, there remains only its interpretation. Professor Obermaier begins it by stating that it does not conform to any true type of steatopygia probably meaning that it conforms to no known type of racial fatness. Pathologically however the case seems probably of interpretation.

As we look at the figurine we see that it represents a middle aged woman of an extreme obese type. The adipose tissue is distributed in the breasts, abdomen and hips and mons veneris. The neck is short and stocky. The shoulders, arms and legs are not obese.

It becomes evident that this is a case of pathologic obesity. Pathologic obesity is divided into two general groups, exogenous and endogenous. Exogenous obesity is the acquired form which results from excessive food and insufficient exercise, endogenous obesity is the result of a disturbance of one or more of the endocrine glands. Endogenous endocrine obesity is further subdivided into hypothyroidism, hypopituitarism, hypogonadism, pluriglandular and cerebral types. Each of these types has its characteristics which leads to its differential diagnosis. A complete discussion of these characteristics is beyond the scope of this paper. For our purpose it is sufficient to describe the characteristics of the case that concerns us. Falta states under his discussion of Hypophyseal Dystrophy that "the accumulation of fat is chiefly localized to the hips, the buttocks, the mons veneris and the mammae." This description of the localization of excess fat conforms to the localization of the excess fat in the figurine of the Aurig-

nacian woman which dates back about 20 000 years. However in the absence of clinical data it is not possible to make an exact diagnosis. Whether this is a pure case of pituitary disease or whether it is a case of pluriglandular disease cannot be determined, but in all probability the pituitary is involved.

The interpretation of disease from characteristics conveyed in figurines, statues, paintings and other descriptive material has nothing of the unusual in it. There exists a large medical literature dealing with this subject.

In attempting to analyze the Aurignacian figurine we assume, of course, that the artist was faithful in reproducing the characteristics of his subject. Paleolithic man of this period was a skilled artist. Some of his polychrome paintings of animals are excellent likenesses of the subjects portrayed. With reference to the Aurignacian Man, Pirsson and Schuchert state

"Armed with better weapons of the chase and a wider knowledge of their use, the Aurignacians were able to take better advantage of their environment. Under these circumstances, they had more ease and time for reflection and we witness in them the birth of the fine arts. Sculpture and drawing appear almost simultaneously and later comes painting. This art we find well preserved in the caves of France and Spain, the art of one period being overlaid by that of later times and as time goes on the workmanship is greatly improved. Animals of many kinds are depicted at first outlined in black, then engraved on the walls and even on the ceilings of the dark caves. Later were



added polychromes in red, brown, black and several shades of yellow. The pigments were of varied mineral origin and were mixed with grease. These artists also engraved animals on stone, bone and ivory. The human figure appears only in the later paintings, and in these garmented women are seen herding cattle and men chasing wild animals. Small figurines made of ivory and limestone and usually representing nude women, are of still greater antiquity."

For purposes of comparison with existing prototypes, we are reproducing the photograph of the figurine and some authenticated cases of pituitary disease taken from Cushing's "The Pituitary Body." A study of these photographs will show the striking resemblance of the anatomical distribution of the excess adipose tissue in both the figurine and in the modern prototypes. The writer is indebted to The Hispanic Society of America for permission to re-

produce the photograph of the figurine and to J. B. Lippincott Company for permission to reproduce the photographs of Dr. Cushing's cases of pituitary disease.

#### SUMMARY

A figurine of an Aulignacian woman approximately 20,000 years old was found by Professor Obermaier at Willendorf, Lower Austria, in 1908. The figurine is eleven centimeters in height, made of porous limestone, well preserved and with traces of pink color. It represents a nude woman with largely developed breasts and hips, buttocks and mons veneris. The distribution of the excess adipose tissue indicates the presence of a pathologic obesity which is probably endocrine in origin. It conforms anatomically with the distribution of excess fat encountered in dysfunction of the pituitary gland. It probably represents a case of pituitary dysfunction. Man's infirmities are as old as man.

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## Editorial

### *THE ANNUAL CLINICAL MEETING*

Next month in Baltimore the College will hold its Fifteenth Annual Clinical Meeting. We are approaching that period when we might be said to be reaching our adolescence. The early struggles of organization are over. The College has shown that it has a definite place in the medical structure of the country; it has survived all opposition and destructive criticism, and now approaches its manhood with confidence and with the optimism and constructive eagerness of youth. It is beginning to feel its strength and looks about for some satisfying outlet for its growing vigor and energy. Growing pains manifest themselves. What shall be its ultimate function? Has it ahead of it a more sharply defined position in the medical life of the country than it now possesses? It has now a highly perfected organization which is working smoothly and successfully; it increases its size each year at a normal and healthful rate; it conducts a yearly meeting the last several sessions of which have distinguished themselves as offering the best and most stimulating programs of any medical association in the country; its plan of local clinics in the various medical centers in which these annual convocations are held offers a unique opportunity to its Fellows and Associates for an intimate

contact with the clinical leaders of the country, it publishes a Journal, the usefulness and influence of which extend far beyond the confines of the College and its members, and it has recently stimulated medical research in internal medicine by the establishment of the John Phillips Memorial Prize. When we have counted these achievements off on our fingers we have told the story of the College and its work up to the present time. Only in one, but that a very important way, has the College had any spiritual influence upon Internal Medicine in America. The mere fact of the College, a selection of physicians for superior worth and attainments, has a very definite influence in the forming of medical ideals throughout the country in creating a professional standard. This influence, though impalpable and immeasurable, is none the less a very real power in determining the social position of the internists of the country, and social position is a very potent factor in the determination of life principles and aims. But this influence of the College is wholly intrinsic, invested in it primordially by virtue of its very existence, and not the result of a conscious and self-directed effort at influencing the trend of medical thought among the Fellows and Associates, and through them among the members of the profession as a whole. It seems to the writer

that this constitutes the chief problem of the College at the present time. Is the College to be satisfied with what it has already accomplished? Is it to go forward year after year, content with its splendid body of representative internists, its successful annual meetings and its journal, and leave no other imprint upon the evolution of medical practice in this country? The writer is sure that the same thought has come to other members of the College in the last year. After all, it has been very fortunate that the energies of the College have been so far expended in perfecting and safeguarding its organization, and in building a firm foundation for whatever superstructure it may later see fit to add. Fortunately, in these years of development, the College has been singularly free of that type of medical politics which is the reproach of the majority of American medical organizations. The one political aim animating its officers and members has been, up to the present moment, concerned wholly with the establishment of the College on a perfectly sound and safe basis. No ulterior or selfish aims have so far disclosed themselves. Now that the existence of the College has been fully assured, it may be well to consider its future program. What possibilities lie ahead? Into a consideration of these the College should engage itself with great caution and consideration. We have been saved from mistakes by our slowness in developing the functions of the College. We should be in a position to profit through the mistakes made by the American College of Surgeons, and surely we can have no desire to duplicate or

parallel that association, either as to ideals or functions. This is not said in a critical way, but stated simply as a fact. We should be able to accomplish something far more noteworthy and significant for the development of internal medicine than that organization has accomplished for surgery, partly because, coming later, we can more fully evaluate the present-day complexities of the situation in which medicine finds itself. Even in the last few years this situation has been clarified in certain of its aspects through much public discussion of questions primarily medical in character. It is true that we have had Committees on Hospitals, Medical Education, Post-graduate Instruction, etc., but nothing has been accomplished by them, and even some of these committees have passed out of existence. This again may be explained by the fact that all our energies were being expended for purposes of self-preservation. We were certainly not prepared to take up constructive work along any one of these lines. Moreover, is it along any one of these that we wish now to go? Is not machinery already furnished by the American Medical Association, the associations of medical colleges, hospitals, etc., to make adequate surveys and studies of such aspects of these problems, as far as internal medicine is concerned? It does not seem that we would be doing anything more than duplication were we to embark upon a special investigation along any one of these lines. All of the questions of medical education and legislation, and of general medical organization in the country seem to be fully taken care of by these various associations, whose

chief duty it is to attend to these problems. If at any time we do not think that certain aspects referring to internal medicine are receiving due attention at their hands, it is within our privilege to call their attention to the fact, and direct them accordingly. It does not seem probable that the College can make any notable contribution directly to questions of education, hospital administration or medical legislation, but it may do much indirectly, by furnishing a body of opinion favoring or opposing any given principle under discussion. Again I think the College is to be congratulated for having escaped useless duplication of effort and energy along the lines originally planned for it. This brings me back to the original question as to the future program of the College. If we are to take a more active part in guiding medical opinion than our present program indicates, it should be along the line, peculiarly fit and appropriate for this society, of influencing the cultural and spiritual side of the general medical mind. We are living in a period in which the soul of the people as a whole is being strongly stirred in regard to social questions as never before. Indeed our modern State is on trial. Social unrest dominates the entire world. Such questions as the dole, bonuses, relief funds, insurance against illness, age and unemployment, cost of medical care, gratuitous medical service, etc., loom more importantly every day. And hints of State Medicine become increasingly louder and bolder. The experience of many physicians during the present year of depression has been very enlightening. They have been made to realize in no pleasant way

that medical service is a luxury in over fifty per cent of cases, and a luxury that can be foregone. Hence the empty offices and hospital wards of the present time. In times of prosperity, the practitioner is apt to be a little arrogant in his assumption that medical service is an absolute necessity, and will continue no matter what happens. A year like the present one teaches him otherwise. All of the present-day social unrest affects medicine more intimately than it does any of the other professions. So if deep-rooted changes occur in society at large, medicine must inevitably be deeply involved. Are such changes to occur without thought or discussion of the principles concerned? Should they come, will the men of medicine be prepared to adapt themselves to the inevitable changes that will take place in the machinery of medical practice? Not without much pain, I believe. Does it not behoove us to be in touch with the thought-currents of our times, so that we may acquire an intelligent understanding of the principles and points of view under discussion? We must ultimately stand on one or the other side, and our choice should be one dictated by reason and not by prejudice or heredity. This is what I mean when I say that the College should develop the spiritual side of the medical mind in this country. Herein, I believe lies its greatest possibility for good. But this is an intangible program I am at once reminded. Not at all! It would only mean some care and thought in the preparation of our programs, a more serious consideration of speakers on definitely chosen subjects bearing upon the thought-mov-

ments of the day, and an opportunity for the College to freely discuss the points of view presented by these speakers. What is needed is to excite interest among the Fellows in these questions. How barren our programs are as far as they reflect the cultural and philosophical sides of medicine. They are too utilitarian, too didactic—only here and there appears an address that concerns itself with something besides diagnosis, case-histories, and treatment. President Musser's address last year was an exception, but my impression was that too many heard it with unheeding ears. The Annual Meeting of the College offers, however, an opportunity for the exchange of opinion, even more satisfactory than that afforded by its programs, and that is the personal contact of Fellows made possible by this yearly coming together. This is after all the highest function of the College, the bringing together for a week of intimate contact the

elect of the medical internists from all over the country. What an opportunity is here offered for the sympathetic clashing of personalities, for the interchange of idea and viewpoint. If these personal contacts could only be guided to the discussion of the important matters of the day, instead of motor-car and golf. Those subjects are, however, very important and have their place in our lives. Only not too much place, to the exclusion of even more important things, should be given them. Here again our utilitarian program conspires to defeat our highest function. The European societies are much wiser than we, nearly half of the time given up to their annual meeting is devoted to social affairs—that is to cultural matters. And from such meetings, where the flow of soul has had an even chance with the flow of reason, one comes away refreshed in body and spirit, mentally alert, and awake to the pulsings of his times.

# Baltimore As A Medical Center

LAURENCE H BAKER, Ph D *Baltimore, Md*

SINCE its very foundation, the city of Baltimore has constituted a community in which physicians have been peculiarly prominent in which physicians have been outstandingly connected with civic and intellectual advances. It is not surprising, therefore, that Baltimore occupies an enviable place in the history of the development of modern medicine. Its contributions to the three great divisions of medical progress—care of the sick, training of succeeding generations of physicians, investigation into the cause and cure of disease—have been of momentous value and have made themselves felt throughout the world.

A brief sketch of the early progress in medicine that the city has seen may be drawn from John R. Quinan "Medical Annals of Baltimore." There one may learn that Baltimore physicians in 1769, maintained the only inoculating hospital open in America, in 1799 established the sixth State Medical Association in this country, in 1801 disseminated the doctrine of vaccination over the United States, in 1807 established the country's fifth medical college (University of Maryland), in 1830 founded the first College of Dentistry in the world and published the first entirely original work on Dentistry in America; in

1882 established the fourth medical school in the United States for the education of women. In some two pages of fine, continuous print—pages well worth noting—Quinan presents an impressive array of achievements in education, research, and medical and surgical technique. His "Annals," however, cover only the period from 1608 to 1880. The fifty-one years intervening between 1880 and the present added a host of advances no less brilliant and far-reaching.

To enumerate and discuss all these advances would require unlimited space. To present a brief summary it is no exaggeration to set down the following statements. Baltimore supplies the major portion of the physicians of the State of Maryland, and a surprisingly high percentage of the physicians of the entire country including its foreign territories and protectorates. This can be verified by checking the Directory of the American Medical Association. On the faculties of the leading medical schools of the country, on the staff of the Rockefeller Institute for Medical Research in the Public Health Service—even in many of the older institutions abroad—may be found teachers and investigators who secured all or part of their training in Baltimore institutions.

tions Throughout the profession—in both medicine and surgery—there are in use numerous standard procedures, highly effective means of combating discomfort and disease, direct and reliable principles of diagnosis and therapeutics which have had their origin in Baltimore

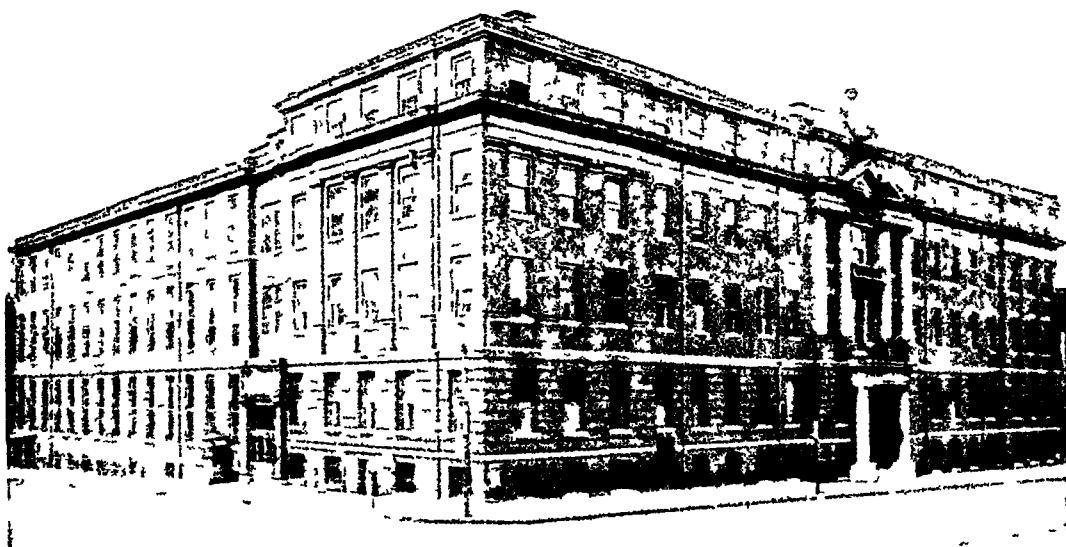
Today the city offers unusual advantages for the student, whether he be aiming at the degree of Doctor of Medicine or seeking further experience and training after attaining that degree For the sick, who come here from all parts of the world, it offers exceptional facilities for care and treatment The city contains two of the country's leading schools of medicine In its inventory of hospitals for Baltimore, the Directory of the American Medical Association lists thirty-five of these institutions

Of the two medical schools, that of the University of Maryland is the older, dating from 1807 It has be-

hind it a long tradition of successful training of practitioners and investigators, today it is the place whence are graduated most of the physicians who attend the sick of Maryland This School of Medicine was one of the first to provide for adequate clinical instruction by the erection, in 1823, of its own hospital, The Baltimore Infirmary Under the name of the University Hospital it still stands on its original site at Lombard and Greene Streets Its present capacity is 275 beds devoted to general medicine, surgery, obstetrics, and the various medical and surgical specialties In connection with the hospital, an extensive out-patient department is conducted, two important features of which are the Outdoor Obstetrical Clinic and the Babies' and Children's Clinic These two perform a valuable service for the public health and social welfare of the community Modernly equipped clinics have been opened re-



UNIVERSITY OF MARYLAND

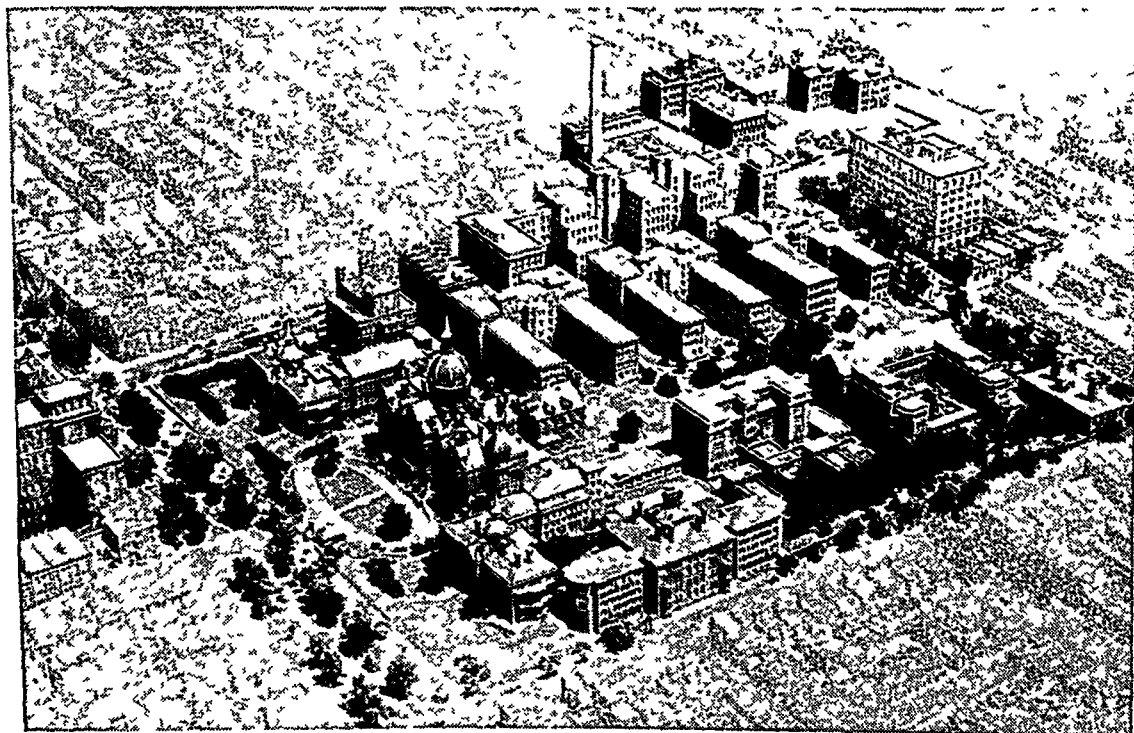


THE UNIVERSITY HOSPITAL

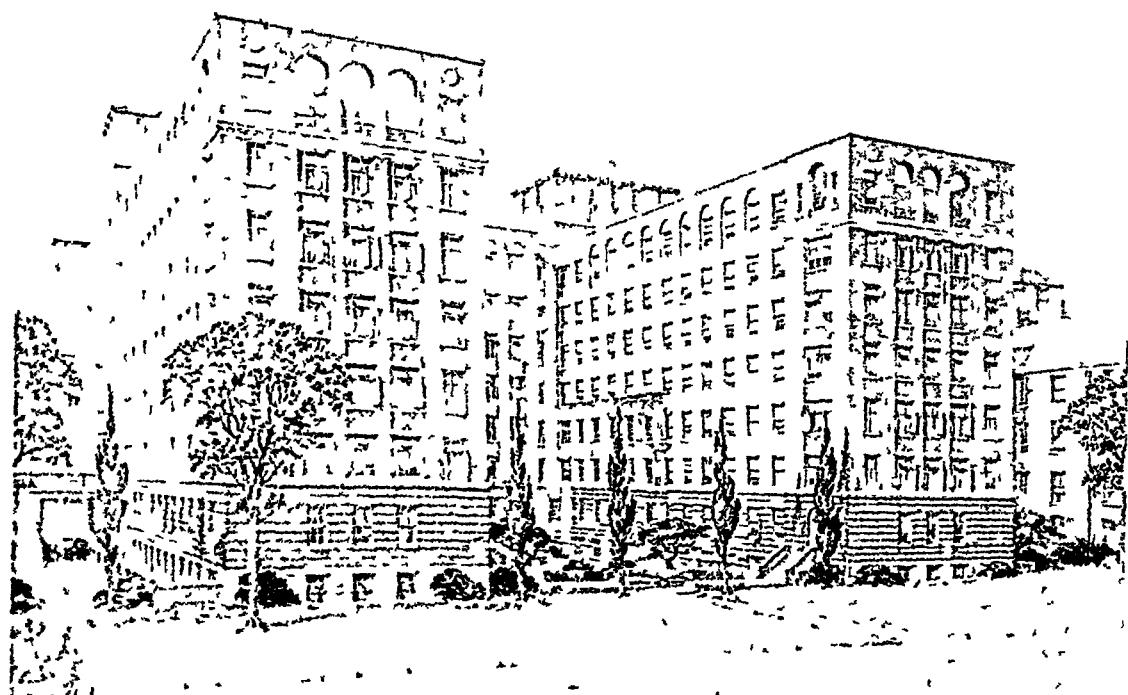


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JOHNS HOPKINS HOSPITAL GROUP



MEDICAL AND SURGICAL CLINICS, JOHNS HOPKINS HOSPITAL

cently at this Hospital for diseases of the nose and throat and for cancer. This year the Hospital put into service an elaborately constructed air-conditioning apparatus which provides facilities for three patients at once, and admits of careful adjustment of the chemical and physical properties of the air to suit the individual patient's needs. This apparatus installed at a cost of \$17,500, is a great advantage in cases of respiratory diseases, and in all the many conditions in which is indicated a ready control of atmospheric temperature, humidity and concentration of oxygen and other gases.

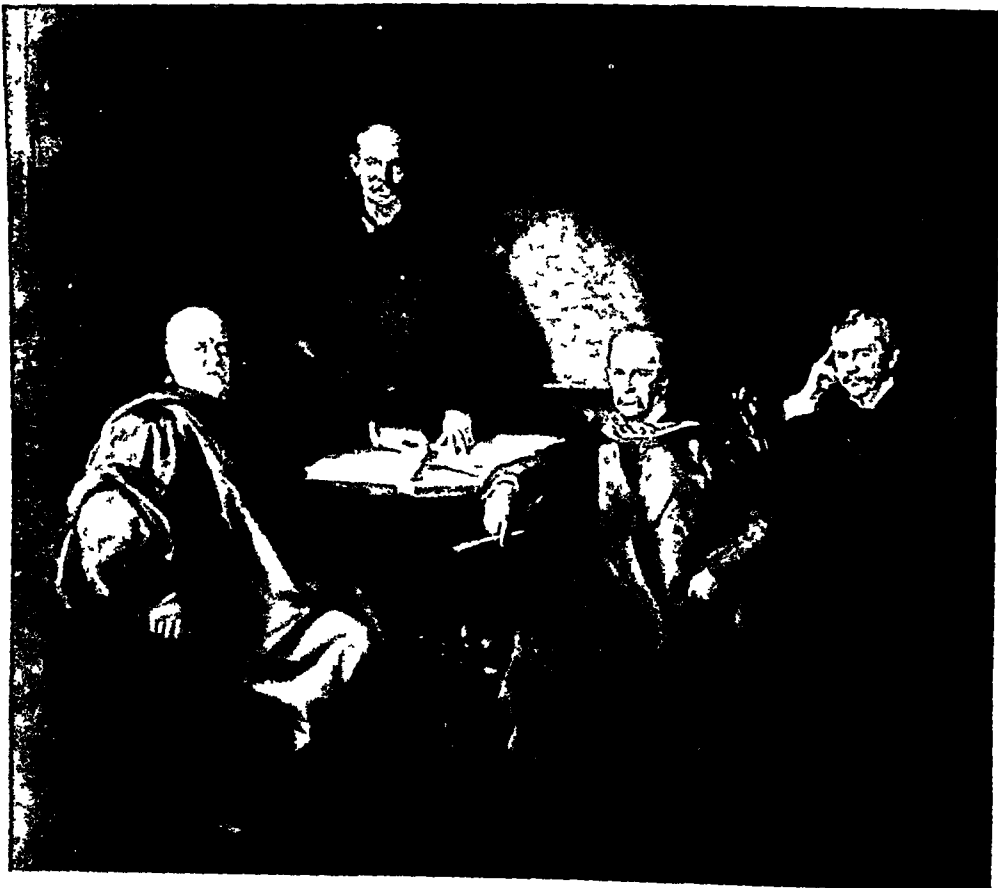
The epochal points in the history of both the University of Maryland School for Medicine and the University Hospital were mentioned in these pages last month. Yet there are countless other contacts between these two institutions and medical progress. How many medical men of today think of the University of Maryland when their attention is demanded for tying both carotids at a short interval in the same subject (W. D. MacGill 1823), ligation of the common iliac artery (W. Gibson, 1812), division of the recti muscles for strabismus (W. Gibson 1822—seventeen years before Diefenbach), removal of pharyngeal polypus (Tiffany 1878), excision of the cervix uteri (Jameson 1823). In the parenthesis are the names of University of Maryland men who performed the operations for the first time as well as the dates they were performed. It seems not unusual that the first school in this country to introduce an independent chain of diseases of women should be the first in

the world to perform a Caesarian Section twice in the same woman, saving mother and child both times. Nor is it surprising that a standard textbook on obstetrics should be written by one of its graduates, J. W. Williams, 1888. In view of the modern popularity of boric acid as an opthalmic antiseptic, it is interesting to note that it received its original application from Samuel Theobald, in 1880 who was a graduate of the University of Maryland. When one thinks of ovariectomy and kindred operations it is well to bear in mind that in 1825 the University of Maryland conferred upon Ephraim McDowell, the father of modern abdominal surgery, his first formal medical degree.

The second medical school, of the city is that of the Johns Hopkins University dating from 1893. The closest cooperation exists between the Johns Hopkins School of Medicine, The Johns Hopkins Hospital and the Johns Hopkins School of Hygiene and Public Health so that these three institutions, covering several acres in the eastern section of the city present one of the world's outstanding centers for medical treatment, teaching and research. Since 1914 the Johns Hopkins School of Medicine has applied the full-time system to its clinical branches, and at the present time all the responsible instructors in Medicine, Surgery, Pediatrics, Psychiatry, Ophthalmology and Obstetrics are salaried persons devoting their entire time to university work. From the opening of the school, the preceptor instructors have always been on this basis.



THE WELCH MEDICAL LIBRARY



SARGENT'S PORTRAIT OF THE FOUR DOCTORS Wm H WELCH, SIR WILLIAM A OSLER,  
HOWARD A KELSEY, Wm S HALSTED

The Johns Hopkins Hospital, which has a separate board of trustees and a separate endowment from that of the university, dates from 1889. In construction, it may be termed one of the pavillion types of hospitals, the several major branches of medicine and surgery being housed in separate buildings. Long corridors, however, make the numerous buildings immediately accessible and facilitate the transportation of patients from one point to another without exposure. In growth, the hospital has paralleled quite closely an accretional epic, starting with the dome-topped, red-brick administration building and adding the numerous separate clinics as scientific advances and new funds made them possible. An interesting account of the growth of both the hospital and the school of medicine will be found in the Appendix of the medical school catalogue.

Under the policy of cooperation between hospital and school, the heads of the main clinical services, as well as the director, are members of the medical faculty. The hospital contains 763 beds, and its capacity will be expanded until a total of 950 is reached. The main clinical pavillions are the Marburg Building for Private Patients, the Henry Phipps Psychiatric Clinic, the Harriet Lane Home for Invalid Children, The James Buchanan Brady Urological Institute, the Woman's Clinic, and the Wilmer Ophthalmological Institute. An independent building, completed in 1923, houses the laboratories of pathology and bacteriology. The Out-Patient Dispensary and Diagnostic Clinic of the hospital was completed in 1927 at a

cost of slightly more than \$1,000,000. This dispensary affords, in the lower floors, ample accommodations for a large number of ambulatory patients, with the necessary teaching rooms. On the fifth and sixth floors of the building are housed the laboratory for clinical microscopy and the various other clinical laboratories, including the Kenneth Dows Tuberculosis Research Laboratory. The topmost floors are devoted to the surgical operating rooms.

In the autumn of 1929, the William H. Welch Medical Library was opened as the intellectual center of the Hopkins medical group. This library possesses every modern facility for the proper care and collection of medical publications, and houses, on its top floor, an Institute of the History of Medicine.

In course of construction at the present time are two clinics which will modernize and augment the clinical facilities in medicine and surgery. When completed, these will be aptly named the Osler Medical Clinic and the Halsted Surgical Clinic. It is, indeed, difficult to think of Hopkins without thinking of the names of Welch, Kelly, Osler, and Halsted. Even if Sargent's painting of the Four Doctors had never been made, every American physician and surgeon would carry their portraits in his consciousness. Both Hopkins and Baltimore are replete with references to them. A striking illustration of this fact is to be found in the name of the building used as library and executive headquarters by the Medical and Surgical Faculty of Maryland—Osler Hall.

A brief description of some of the other hospitals of Baltimore follows

*Baltimore City Hospitals* The Baltimore City Hospitals constitute a group of hospitals founded in 1865, owned by the City of Baltimore, and operated under a single administration. Its component parts are General Hospital, 636 beds, Tuberculosis Hospital, 171 beds, Psychopathic Hospital, 325 beds, Infirmary (Home for the Aged) 854 beds; total 1,986 beds. All beds are free, but if a patient can pay part, he is required to do so. A training school for practical nurses is conducted

by the Hospital. This is a pioneer movement, furnishing excellent ministrants for the great number of persons who require trained care but are unable to afford the expenses of a graduate nurse.

*Bon Secours Hospital* This is a general hospital, founded in 1919 through the generosity of Mr and Mrs George C Jenkins. Situated away from the congested centers of the city, it avoids much of the discomfort of noise. The services embrace medicine, surgery, obstetrics, X-Ray, clinical laboratory. There is



SIR WILLIAM OSLER

an out-patient department and a school of nursing. The hospital contains 65 beds and 12 bassinets.

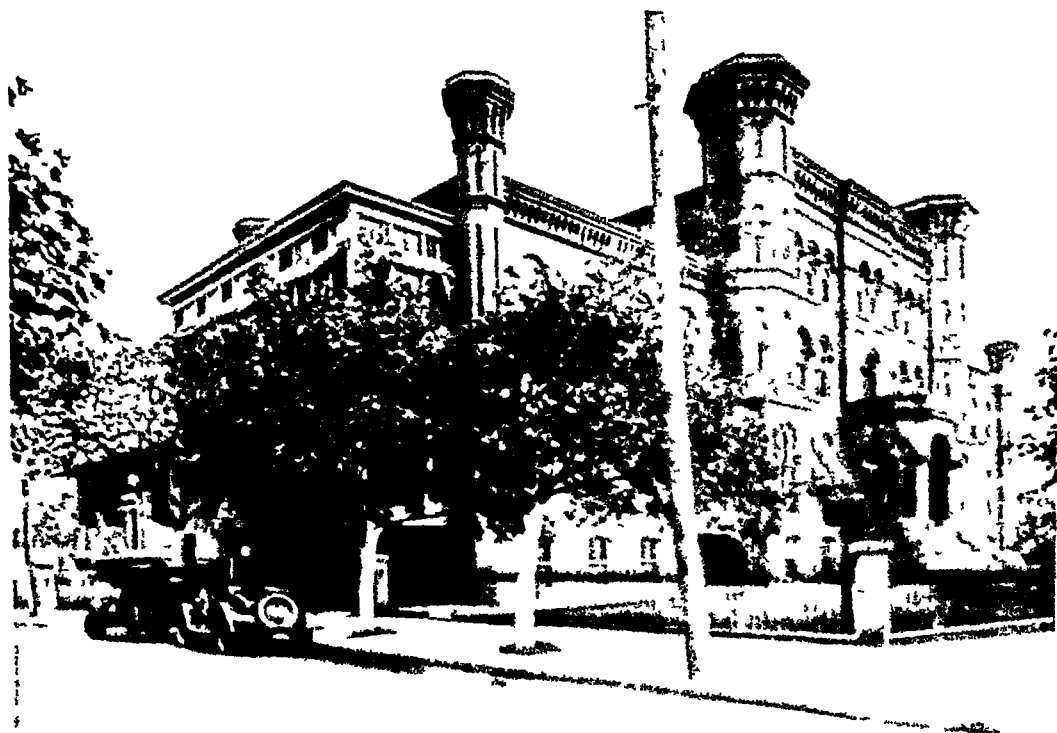
*Children's Hospital School.* The date of foundation of this institution was 1912. It is maintained by State and City appropriations, private contributions and the receipts from pay patients. The number of beds is 130. In addition to the usual services, it provides for occupational therapy. In the coming year are to be added facilities for heliotherapy and physiotherapy. The age limit for patients is 14 years for either boys or girls. Both white and colored patients are admitted.

*Church Home and Infirmary.* This hospital occupies the site of the former Washington Medical College. It dates from 1858. Although non-

sectarian, the hospital is administered by a board of trustees under the Episcopal Church. Its beds number 176, for treatment of acute cases. In addition to the hospital services there is maintained a home for aged women and also a training school for nurses.

*Franklin Square Hospital.* Under the name of the National Temperance Hospital of Baltimore, this institution was incorporated in 1898. The present name was adopted in 1901. Its bed capacity is 129. One of its chief aims is to serve patients of moderate means. In conjunction with the hospital a training school for nurses is maintained.

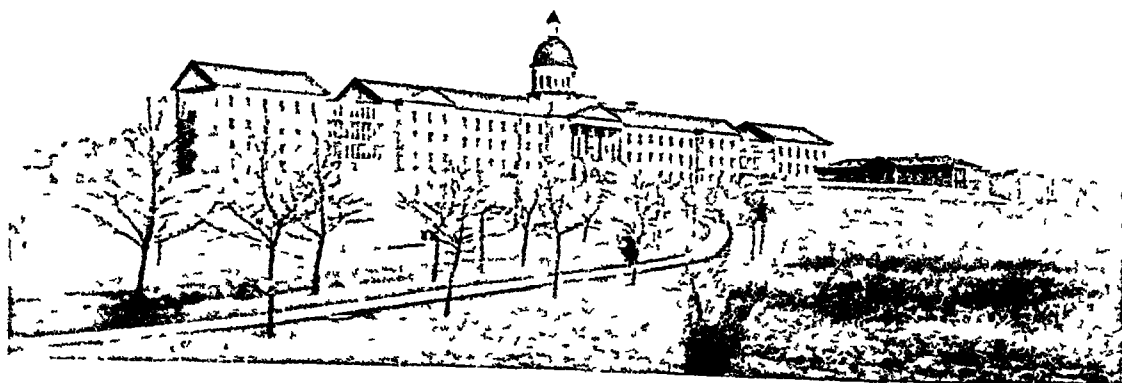
*Hospital for the Women of Maryland.* This is the only hospital in the State devoted exclusively to the care



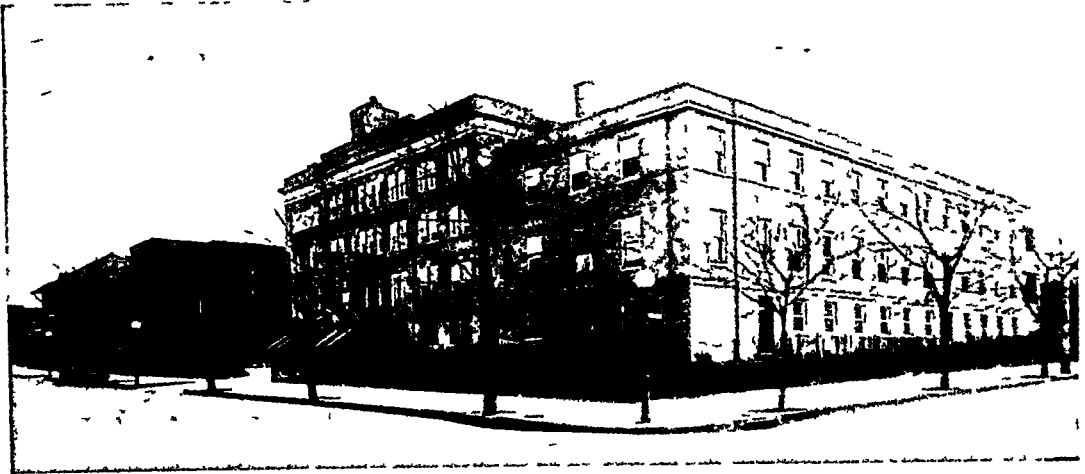
WEST BALTIMORE GENERAL HOSPITAL



SOUTH BALTIMORE GENERAL HOSPITAL



BAY VIEW (CITY HOSPITALS)



BON SECOUR HOSPITAL

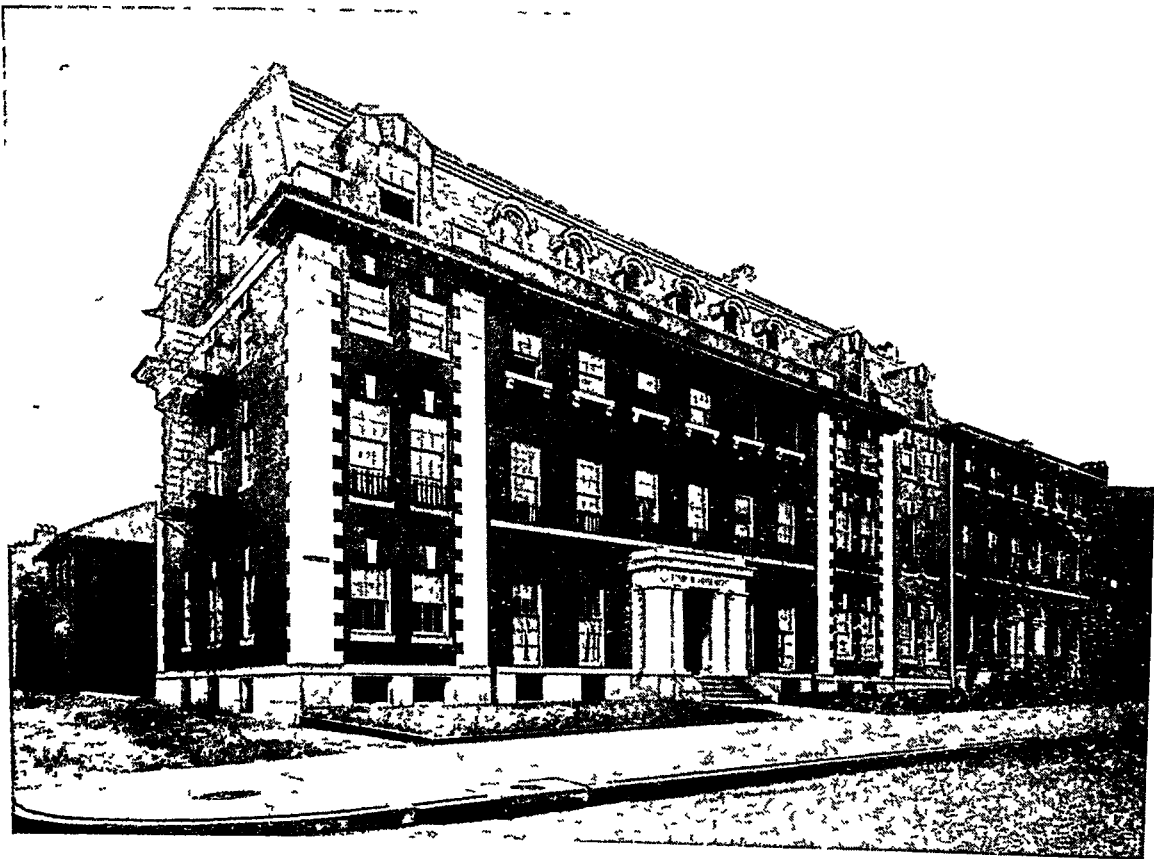


CHILDREN'S HOSPITAL SCHOOL



CHURCH HOME AND PARSONAGE





FRANKLIN SQUARE HOSPITAL



HOWARD A KELLY HOSPITAL



HOSPITAL FOR WOMEN OF MARYLAND (WOMEN'S HOSPITAL)



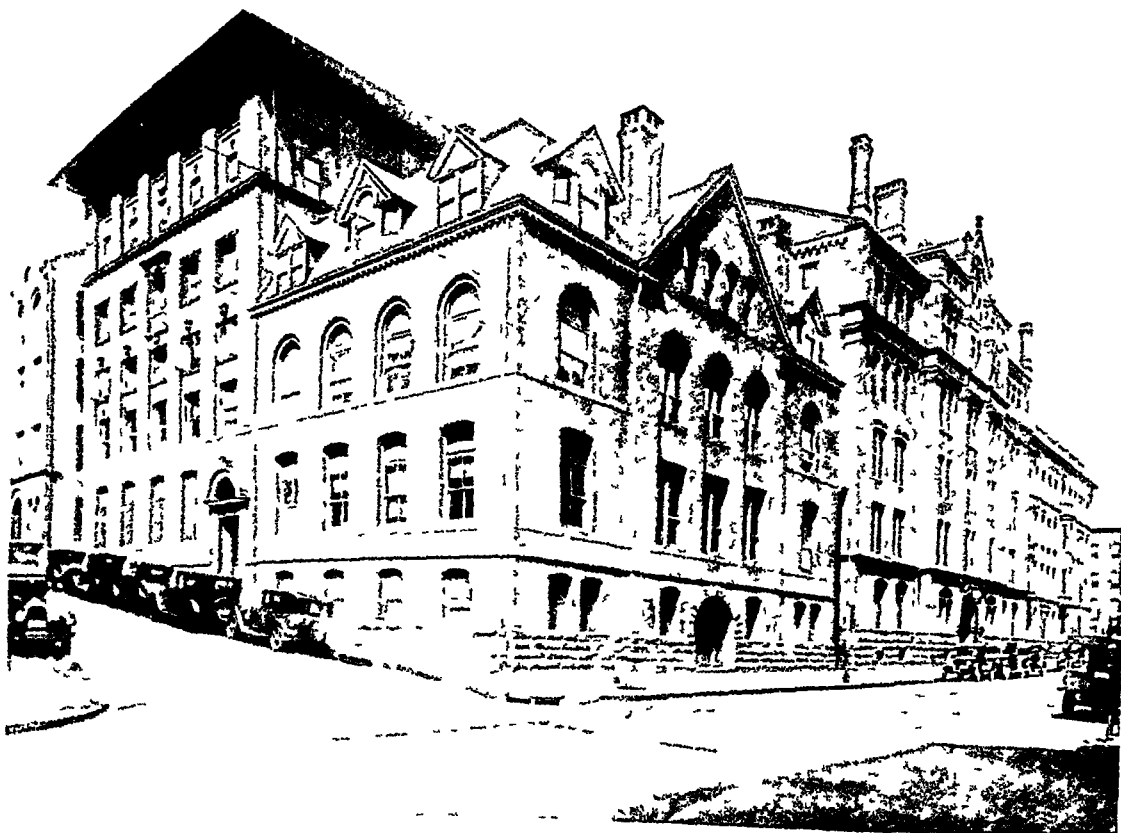
MARYLAND GENERAL HOSPITAL

of sick women It was incorporated in 1882, and at the present time contains 111 beds and 24 bassinets Among its many services are a nurses training school and facilities for post-graduate work in the diseases of women

*Howard A Kelly Hospital* Established in 1882, this hospital has 35 beds and is engaged principally in radiological and gynecological work Longer than any hospital in the country it has possessed a substantial supply of radium, its present stock of this precious and potent metal being over five grams Employing the latest deep therapy X-Ray apparatus and the most modern measuring appliances

for both radiological and X-Ray, it is in an unusually favorable position to do all radiological work

*James Laurence Keenan Hospital* In addition to being a hospital, this institution is also an industrial school for children It contains 62 beds for the active treatment of orthopedic conditions Recently its facilities have been increased by a new building for operating and physiotherapy of bone and joint cases Situated on an estate of 75 acres, it has all the advantages of country air and sunshine A number of the beds are endowed, others are available for private cases, still others are supported by the city and the state



MERCY HOSPITAL



PROVIDENT HOSPITAL

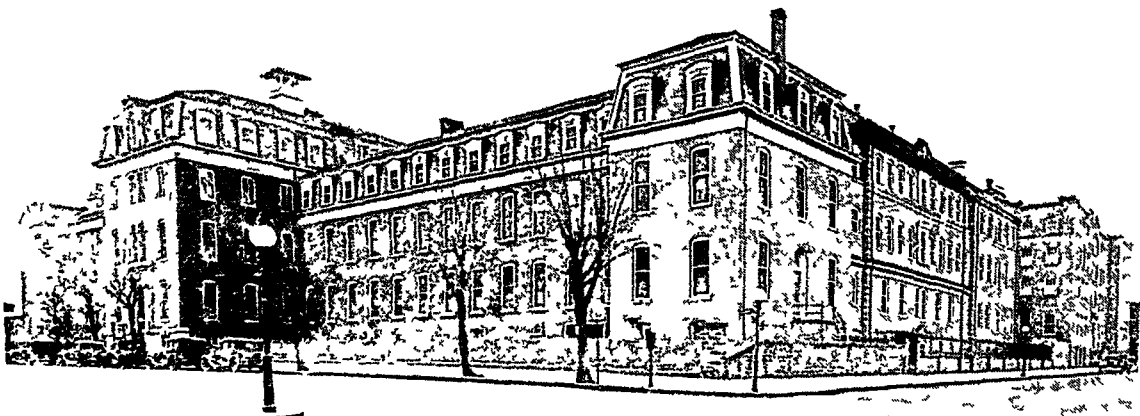


ST. ANNE'S HOSPITAL

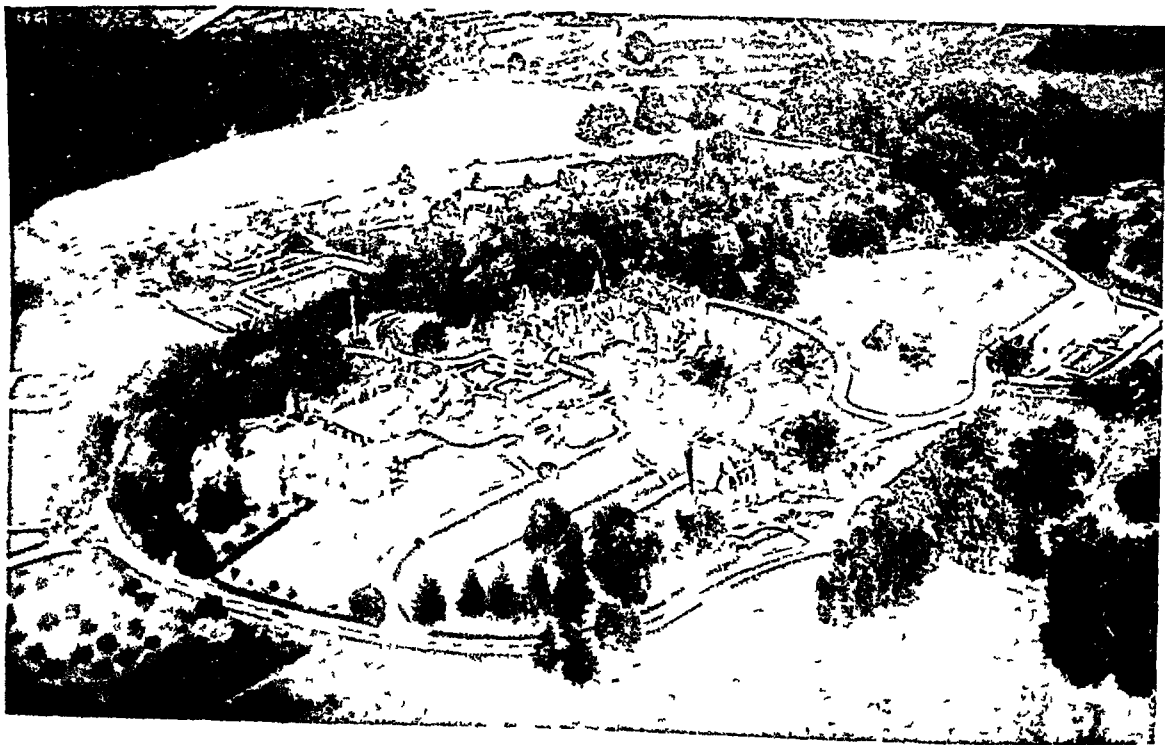
*Maryland General Hospital* Owned and operated by the Methodist Hospital Association, Inc., this is a general hospital of 230 beds. Every modern facility is included for surgical and medical measures, and there is a modern department of light therapy. An active out-patient department and

a nurses training school are maintained.

*Mercy Hospital* Mercy Hospital, as its name implies, is a general hospital conducted by the Sisters of Mercy. It has 90 private rooms and 185 beds available for semi-private and ward patients. Through its affilia-



ST JOSEPH'S HOSPITAL



SHIPPARD & ENOCH PRATT HOSPITAL

tion with the University of Maryland, Mercy Hospital's clinical material, both in its wards and in its out-patient department, is utilized for teaching purposes. Through the generosity of Dr. Waitman F. Zinn, the hospital's facilities have been increased this year by a modern bronchoscopic clinic.

*Provident Hospital and Free Dispensary* This hospital contains 125 beds, together with modern operating room, delivery room and X-Ray facilities. It fills a great need in caring

for numbers of the sick in Baltimore's fairly large colored population, offering opportunities for internship for graduates of colored schools, and training of colored nurses. In this, it performs a valuable service for the promotion of hygiene among the several states near Maryland in which there is a high percentage of Negroes. Although a goodly number of those admitted are pay patients, much of its work is on a charity basis. The building it occupies is the old site of the Union Memorial Hospital (form-



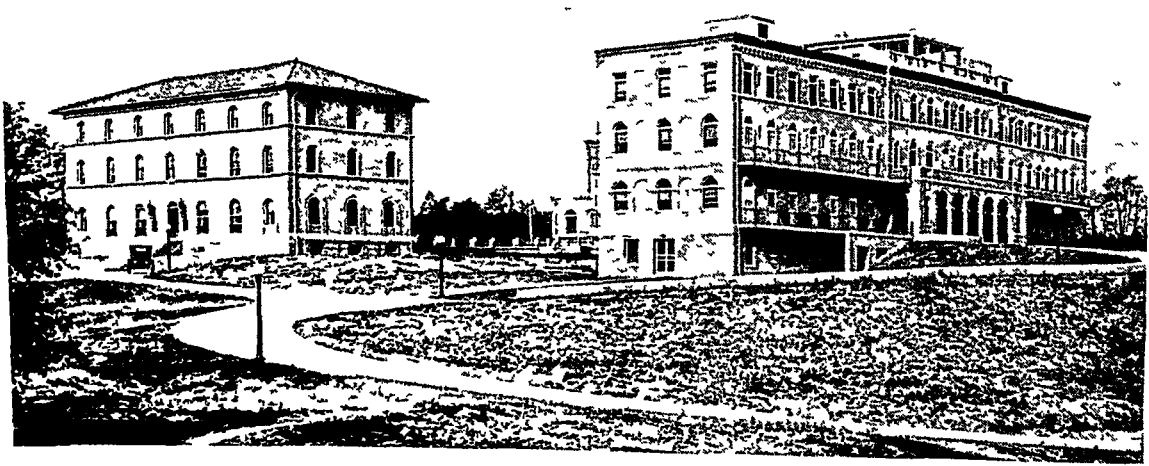
PROVIDENT HOSPITAL

erly the Union Protestant Infirmary) It has been a colored hospital for the last three or four years

*St Agnes Hospital* The Sisters of Charity of St. Vincent de Paul conduct this hospital on Mt Dougherty, Caton and Wilkins Avenues It is a general hospital with 205 beds and a separate maternity unit It dates from 1865 Its out-patient department,

recently reorganized, does excellent work among the poor of the vicinity

*St Joseph's Hospital* This hospital, founded by the Sisters of the Third Order of St Francis, Philadelphia Foundation, dates from 1865 It contains 278 beds and does a large amount of charity work, both in the hospital itself and in the out-patient department



SYDENHAM HOSPITAL



THE UNION MEMORIAL HOSPITAL. INCORPORATED 1854 REBUILT 1923



U S MARINE HOSPITAL



THE FREDERICK BAUKENSCHMIDT MEMORIAL BUILDING (1922)



*Sheppard & Enoch Pratt Hospital* The Sheppard and Enoch Pratt Hospital was founded through the generosity of Moses Sheppard in 1853. In 1903, its endowment was materially increased by Enoch Pratt, a Baltimore philanthropist, hence the two names in its appellation. Today the hospital contains 250 beds and does considerable benevolent work which, in the main, is confined to the residents of Maryland. The work of the hospital is entirely in the field of psychiatry, chiefly in the acute and recoverable illnesses. Habit cases, and cases of undoubted chronicity are not retained. Several members of its staff are included in the faculty of the University of Maryland School of Medicine. It offers facilities for giving specialized experience, both by physicians and nurses. The site of the hospital is on a tract of 411 acres lying between Charles Street and York Road, some twenty-five minutes by automobile from the center of the city.

*The Sinai Hospital* The Sinai Hospital began its existence 63 years ago as the Hebrew Hospital. In 1926 it was entirely renovated. A new pavilion was constructed and the old building was rebuilt for ward work. The cost of the renovation totaled something like a half a million dollars. The number of beds available is 271. The Hebrew Hospital is in the Eastern portion of the city and is a definite element in the great Medical Center developing around Wolfe and

Monument Streets. In addition to the usual services it contains departments of Hydrotherapy, Electrocardiography and Occupational Therapy. A feature of its out-patient department in connection with children is the provision for the necessary convalescent care at the Happy Hills Convalescence Home.

*Sydenham Hospital* This is the municipal hospital for contagious diseases. Operated under the City Health Department, it is entirely free to local residents. The bed capacity is 110. Much of its clinical material is utilized by the city's two medical schools.

*Union Memorial Hospital* Incorporated originally in 1854, this hospital was rebuilt in 1923. The bed capacity is 289. In addition to the usual modern facilities, this hospital contains a wing built and furnished especially for persons of modern means. Both the structure and the endowment of this wing are the gifts of Mr. Frederick Bauerschmidt, a Baltimore philanthropist.

Were the space available, it would be pleasant to mention the outstanding points in connection with all of Baltimore's many hospitals. To do so, however, would run into considerable length, and even then might omit many valuable salient factors. Suffice it to say that the city offers an abundance of hospital facilities to engage the attention and interests of both the clinician and the laboratory man.

# College News Notes

## FINAL PROGRAM

### FIFTEENTH ANNUAL CLINICAL SESSION—AMERICAN COLLEGE OF PHYSICIANS

GENERAL SESSIONS  
Baltimore, Md—March 23-27, 1931

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OPENING GENERAL SESSION  
Monday, March 23 1931, 2 00 O'clock

#### *The Alcazar*

#### 1 Addresses of Welcome

Joseph S Ames, President of Johns Hopkins University  
Raymond A Pearson, President of the University of Maryland  
J M H Rowland, President of the Medical and Chirurgical Faculty of Maryland  
Louis P Hamburger,\* President of the Baltimore City Medical Society

#### 2 Reply to Addresses of Welcome

Sydney R Miller\* President of the American College of Physicians

### SYMPOSIUM ON GASTRO-INTESTINAL DISEASE

#### 3 The Clinical Significance of So-Called Chronic Appendicitis

Julius Friedenwald\* Baltimore, Md  
Theodore H Morrison\* Baltimore Md

#### 4 The Early Diagnosis of Neoplasms of the Digestive Tract

Thomas R Brown\* Baltimore Md

#### 5 Gastric Secretion

A study of electrolytic changes of gastric juice during various phases of secretion in connection with simultaneous corresponding changes in the blood and urine. Also a report on some organic constituents heretofore unreported. (Slides and Charts)  
Law Martin\* Baltimore Md

#### 6 Studies on the Mechanism of the Pain of Peptic Ulcer (Slides)

Fred M Smith\* Iowa City Iowa

#### 7 Rheumatoid Arthritis (Slides)

Russell I Cecil New York, N Y  
(Guest)

\*F A C P

SECOND GENERAL SESSION  
Monday Evening, March 23, 1931, 8 30 P M

*The Alcazar*

Presiding Officer  
Maurice C Pincoffs,\* Baltimore, Md

### SYMPOSIUM OF HEART DISEASE

- 1 Variation in Manifestations on Rheumatic Fever in Relation to Climate (Slides)  
Warfield T Longcope,\* Baltimore, Md
- 2 On Some Phases of Endocarditis (Charts)  
William S Thayer,\* Baltimore, Md
- 3 Chronic Myocardial Insufficiency Chronic Non-Valvular Cardiac Diseases and its  
Therapeutic Management (Slides)  
Henry A Christian,\* Boston, Mass
- 4 The Causation of Cardiac Pain  
Alexander Lambert, New York, N Y  
(Guest)
- 5 The Therapeutic Use of Oxygen in Heart Disease (Slides)  
Alvan L Barach, New York, N Y  
(Guest)

THIRD GENERAL SESSION  
Tuesday, March 24, 1931, 9 A M

*The Alcazar*

Presiding Officer  
George Morris Piersol,\* Philadelphia, Pa

- 1 The Reaction to Nitrites in the Anginal Syndrome and Arterial Hypertension (Slides)  
Alvan M Burgess,\* Providence, R I
- 2 The Insulin Coefficient, and Improved Method for the Clinical Control of Diabetes  
Mellitus (Slides)  
John R Williams,\* Rochester, N Y
- 3 An Evaluation of the Skin Test in Allergy (Slides)  
Harry L Alexander, St Louis, Mo  
(Guest)
- 4 The Trend in Cerebral Localization (Slides)  
Lowells F Barker,\* Baltimore, Md
- 5 Spontaneous Subarachnoid Haemorrhage  
A Report of Twenty-Nine Cases (Slides)  
Wardner D Aver,\* Syracuse, N Y

INTERMISSION  
PLEASE VISIT THE EXHIBITS!

- 6 Post-Vaccination Encephalitis (Slides)  
Charles Armstrong Surgeon, USPHS, Washington, D C  
(Guest)
- 7 The Many-Sided Question of Protein in Nephritis (Slides).  
William S McCann,\* Rochester N Y

- 8 Circulatory Adjustments in Cardiovascular Diseases (Slides)  
Soma Weiss,\* Boston, Mass
- 9 The Response of the Cardiovascular System to Respiratory Strain A Measure of Myocardial Efficiency (Slides)  
Allan Eustis,\* New Orleans, La

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FOURTH GENERAL SESSION

Tuesday Evening, March 24, 1931, 8 30 P M

*The Alcazar*

Presiding Officer

William Gerry Morgan,\* Washington, D C  
President of the American Medical Association

SYMPOSIUM ON PUBLIC HEALTH,  
MEDICAL PRACTICE AND MEDICAL ECONOMICS

- 1 The Influence of the Practitioner of Medicine in Guiding the Public towards Health (Charts)  
Haven Emerson, New York, N Y  
Professor of Public Health Administration, College of Physicians and Surgeons, Columbia University  
(Guest)
- 2 The Proper Relations between the Practicing Physicians and Health Officers  
Felix J Underwood,\* Jackson, Miss  
President of the Southern Medical Association
- 3 The Hospital—Its Relation to the Community and to the Medical Profession  
Winford H Smith, Baltimore, Md  
Director of the Johns Hopkins Hospital  
(Guest)
- 4 Speaker to be Announced

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FIFTH GENERAL SESSION

Wednesday, March 25, 1931, 9 A M

*The Alcazar*

Presiding Officer

John H Musser,\* New Orleans, La

- 1 Complement Fixation in the Diagnosis of Amoebiasis  
Charles F Craig,\* Colonel, (M C), U S Army, Washington, D C
- 2 The Treatment of Recurrent Erysipelas (Slides)  
Harold J. Amoss, Durham N C  
(Guest)
- 3 Observations on Pneumococcus Type III Pneumonia (Slides)  
Francis G Blake,\* New Haven, Conn
- 4 Experimental Pathology of the Liver. (Slides)  
Jesse L Bollman, Rochester, Minn  
(Guest)
- 5 Clinical Aspects of Portal Cirrhosis (Slides)  
Albert M. Snell,\* Rochester, Minn

INTERMISSION  
PLEASE VISIT THE EXHIBITS!

- 6 The Morbid Anatomy of the Diaphragm (Slides).  
Baldwin Lucké, Philadelphia, Pa  
(Guest)
- 7 Pneumoconiosis; Clinical and X-Ray Aspects (Slides)  
H. R. M. Landis,\* Philadelphia, Pa
- 8 Endo-Bronchial Manifestations of Pulmonary Disease Observation on Broncho-  
scopic Diagnosis and Treatment (Lantern slides and moving picture film)  
Gabriel Tucker, Philadelphia, Pa  
(Guest)
- 9 Heliotherapy (Moving picture)  
Alexius M. Forster, Colorado Springs, Colo  
(Guest)

Evening, 8 00 O'clock

*The Alcazar*

CONVOCATION OF THE COLLEGE

The General Profession and such of the general public as may be interested are cordially invited. No special admission tickets are required. Evening dress is recommended.

1 Convocation Ceremony

2 President's Address,

Sydney R. Miller, Baltimore, Md

*Reception to New Members*

An informal Reception to new members will follow immediately after the Convocation exercises, at the back of the Auditorium. Newly inducted Fellows should sign the Roster and secure their Fellowship Certificates during the interim between the Convocation and the Reception.

SIXTH GENERAL SESSION

Thursday, March 26, 1931, 9 A. M.

*The Alcazar*

Presiding Officer

Francis M. Pottenger,\* Monrovia, Calif

SYMPOSIUM ON ENDOCRINE DISORDERS

NOTE Papers will be limited to 15 minutes  
No intermission possible on account of  
Annual Business Meeting

- 1 Pathological Classification of Goiter and its Clinical Significance (Slides)  
Wm. Carpenter MacCarty,\* Rochester, Minn
- 2 The Management of Patients with Extreme and Atypical Hyperthyroidism (Slides)  
Frank H. Lahey, Boston, Mass  
(Guest)

\*F. A. C. P.

- 3 Clinical Studies of Hyperthyroidism before and after Subtotal Thyroidectomy  
Henry M Thomas, Jr,\* Baltimore, Md  
William F Rienhoff, Jr, Baltimore, Md  
(Guest)
- 4 The Use of Quinidine Sulphate in the Treatment of Cardiac Irregularities Due to Hyperthyroidism  
John P Anderson,\* Cleveland, Ohio
- 5 The Vital Hormone of the Adrenal Cortex (Slides)  
Frank A Hartman, Buffalo, N Y  
(Guest)
- 6 The Relation of the Parathyroid Glands to Calcium Metabolism (Slides)  
David Preswick Barr,\* St Louis, Mo
- 7 The Etiology and Treatment of Diabetes Insipidus (Slides)  
Thomas B Fletcher,\* Baltimore, Md
- 8 Metabolic Factors of Value in the Treatment of Obesity (Slides).  
Frank A Evans,\* Pittsburgh, Pa
- 9 The Questionable Nature of "Luxuskonsumption" (Slides)  
L H Newburgh,\* Ann Arbor, Mich

THE ANNUAL GENERAL BUSINESS MEETING of the College will be held immediately after the last paper All Masters and Fellows are urged to be present Official reports from the Executive Secretary and Treasurer will be read, new Officers, Regents and Governors will be elected, and the President-Elect, Dr S Marx White, will be inducted into office

Evening, 7 30 O'clock

*Lord Baltimore Hotel*

### THE ANNUAL BANQUET OF THE COLLEGE

(Procure tickets at the Registration Bureau)

Dr Lewellys F Barker,\* Baltimore, will act as Toastmaster  
Dr Wm H Welch, Professor of the History of Medicine at Johns Hopkins University School of Medicine, will deliver the chief address  
Following the Banquet, there will be dancing for those who wish to remain

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### FINAL GENERAL SESSION

Friday, March 27, 1931, 9 A M

*The Alcazar*

Presiding Officer

S Marx White,\* Minneapolis, Minn

- 1 Tachycardia Its Etiology, Prognosis and Treatment (Slides).  
Chas W Barrier, Fort Worth, Texas  
(Guest)
- 2 Allergic Migraine Based on the Study of 200 Cases (Slides)  
Ray M Balyeat,\* Oklahoma City, Okla
- 3 Chronic Changes in Chronic Arthritis (Slides)  
W Howard Dickson, Toronto, Canada  
(Guest)

\*F A C P

## SYMPOSIUM ON ANEMIA

- 4 Agranulocytosis Its Classification, with Cases and Comments Illustrating the Leucopenic Trend from 8,000 Blood Counts in the South (Charts)  
 Stewart R Roberts,\* Atlanta, Ga  
 Roy R Kiacke, Atlanta, Ga  
 (Guest)

## INTERMISSION

## PLEASE VISIT THE EXHIBITS!

- 5 Diet as a Factor in the Etiology of Anemia (Slides)  
 Richard A Kern, Philadelphia, Pa  
 (Guest)
- 6 The Anemias Associated with Gastro-Intestinal Disorders Clinical Considerations and the Value of Iron in their Treatment (Slides)  
 Chester S Keefer, Boston, Mass  
 (Guest)
- 7 Clinical and Experimental Observations on the Treatment of Pernicious Anemia with Ventriculin and with Liver Extract (Slides)  
 Cyrus C Sturgis,\* Ann Arbor, Mich  
 Raphael Isaacs, Ann Arbor, Mich  
 (Guest)
- 8 The Adequate Treatment of Anemia (Slides)  
 George R Minot,\* Boston, Mass  
 William B Castle, Boston, Mass

## BALTIMORE PROGRAM

## SPECIAL CLINICS AND DEMONSTRATIONS

Clinics and demonstrations will be held in the afternoons from 2 00 to 5 00 daily, Tuesday to Friday, inclusive

*Tickets will be required for each and every one of the special clinics, ward rounds and demonstrations* The co-operation of everyone in securing their clinic tickets will assist greatly in distributing the attendance according to the capacity of each program It is self-evident that a ward round arranged for twenty-five will lose its value for all if forty or fifty are present Ticket registration naturally is the only effective method of keeping the attendance within the capacities indicated

*To all members of the College, registration blanks for the clinics and demonstrations will be distributed with the final program* These registration blanks should be filled out and returned to the Executive Secretary Upon receipt of your application for clinic reservations by the Executive Secretary, proper tickets will be selected and held for you at the Registration Bureau at Baltimore Reservations by mail cannot be made after March 15, but reservations may be made in person at the Registration Bureau on the evening preceding any clinic day *Guests will kindly register for clinics at the Registration Bureau upon arrival at Baltimore*

Tuesday, March 24, 1931

**A**      **JOHNS HOPKINS UNIVERSITY SCHOOL OF MEDICINE**

Physiology Building No 25  
(Washington and Monument Sts)  
Lecture Room—Second Floor  
(Capacity—90)

Program from the Department of Anatomy of the School of Medicine and the Department of Embryology of the Carnegie Institution of Washington (Program repeated on Thursday)

- 2 00-2 20 Endocrines and Reproduction  
C G Hartmann
- 2 20-2 40 Development of the Mammalian Egg  
G L Streeter
- 2 40-3 00 Behavior of Living Cells (Motion Pictures)  
W H Lewis
- 3 00-3 30 Human Growth and Human Evolution  
A H Schultz
- 3 30-5 00 Visit to the Laboratories of the Department of Anatomy (Building No 22), and the Carnegie Institution, Department of Embryology (Building No 23, Second Floor)
- 

**B**      **JOHNS HOPKINS HOSPITAL**  
Department of Pathology  
(No Program on Tuesday)**C**      **JOHNS HOPKINS HOSPITAL**  
Department of Medicine  
Building No 15, Medical Amphitheatre, 1st Floor  
(Capacity—170)

- 2 00-2 45 Clinic  
J C Meakins, Montreal
- 2 45-3 30 Clinic  
W T Longcope
- 3 30-4 15 Medical-Surgical Conference  
T R Brown and Dean Lewis
- 

**D**      **JOHN HOPKINS HOSPITAL**  
Department of Medicine  
Building No 11, Osler Clinic  
(Capacity—25 to each ward)  
\*Ward Rounds

- \*D-I Ward I —2 00-3 00 E P Carter  
3 00-4 00 L V. Hamman
- \*D-II Ward II —2 00-3 00 T B Fletcher  
3 00-4 00 E C Andrus
- \*D-III Ward III—2 00-3 00 S R Miller  
3 00-4 00 W. S. Tillett
- \*(Separate tickets for each of these three rounds)



E

## JOHNS HOPKINS HOSPITAL

Department of Medicine

Out-Patient Division

Building No. 14, Third Floor, Room No 302

(Capacity—90)

- 2 00-2 20 Bundle Branch Block   Exhibition of Cases  
J T King, Jr
- 2 20-2 40 Non-bacterial Bronchopneumonia   A case report  
H M Thomas, Jr.
- 2 40-3 00 Maternal Lumbo-sacral Plexus Injury during Childbirth  
Orthello R Langworthy
- 3 00-3 20 The Treatment of Syphilis  
J E. Moore
- 3 20-3 40 Syphilitic Juxta-Articular Nodules  
H H Hopkins
- 3 40-4 00 Syphilitic Aortitis  
J C Reisinger
- 4 00-4 20 Bone Syphilis  
E D Weinberg
- 4 20-4 40 Practical Considerations of the Wassermann Reaction  
Albert Keidel
- 

F

## JOHNS HOPKINS HOSPITAL

Department of Medicine

Division of Laboratories

Building No 15, First Floor, Room No 9

(Capacity—60)

(Same program repeated on Thursday)

- 2 00-2 20 Sulphaemoglobinaemia  
G A Harrop
- 2 20-2 40 A Liver Function Test with Bilirubin  
G A Harrop
- 2 40-3 00 Present Day Conceptions of Immunity in Syphilis  
A M Chesney
- 3 00-3 20 Rôle of Trauma in the Localization of Syphilitic Lesions  
T B Turner
- 3 20-3 40 Specificity of the Diagnostic Tests for Syphilis  
Harry S Eagle
- 4 00-5 00 Informal Conferences and Demonstrations in Chemical Laboratory of Medical Clinic, 5th Floor, Room No 516, and in Laboratory of Experimental Syphilis, 6th Floor, Room 601
- 

G

## JOHNS HOPKINS HOSPITAL

Department of Obstetrics

Building No 12, Woman's Clinic, Ground Floor

(Capacity—72)

(Same program repeated on Thursday)

- 2 00-2 20 Medical Indications for Sterilization  
J W Williams

- 2 20-2 40 End Results of Chronic Nephritis Complicated by Pregnancy  
H J Stander
- 2 40-3 00 Diabetes and Pregnancy  
C H Peckham
- 3 00-3 20 Blood and Urinary Protein in the Toxemias of Pregnancy  
M J Eastman
- 3 20-3 40 Heart Disease and Pregnancy  
A F Guttmacher
- 3 40-4 00 The Pituitary Gland and the Internal Genitalia  
I Hofbauer
- 4 00-5 00 Informal Conferences in the Laboratories of the Department of Obstetrics, 4th  
and 5th Floors, Woman's Clinic
- 

*H*

## JOHNS HOPKINS HOSPITAL

Department of Pediatrics  
Building No 18, Harriet Lane Home  
(Capacity—100)

- 2 00-2 45 Tuberculosis During the First Year of Life  
E A Park
- 2 45-3 00 Active Immunization against Tuberculosis with Dead Tubercle Bacilli  
F. F. Schwentker
- 3 00-3 15 Treatment of Lye Poisoning  
T C Goodwin
- 3 15-3 30 Effect of Insulin on Mineral Metabolism in Infantile Malnutrition  
M I Rubin
- 3 30-3 45 Prognosis of Nephritis in Children  
H Guild
- 3 45-4-15 Case Presentations
- 4 15-5 00 Visits to Wards, Dispensary and Laboratories of Harriet Lane Home
- 

*I*

## JOHNS HOPKINS HOSPITAL

Department of Psychiatry  
Phipps Psychiatric Institute  
Building No 19, 2nd Floor  
(No Program on Tuesday)

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*J*

## JOHNS HOPKINS HOSPITAL

Department of Surgery  
Building No 14, Seventh Floor, Room 722  
(No Program on Tuesday)

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*K*

## JOHNS HOPKINS HOSPITAL

Department of Ophthalmology  
Wilmer Ophthalmology Institute  
Building  
(Capacity—110)

- 2 00-2 15 Syphilitic Ocular Lesions  
Alan C Woods
- 2 15-2 30 Ocular Changes in Disturbances of Lipid Metabolism  
Jonas Friedenwald

- 2 30-2 45 Modern Conception of Retinal Detachment with its Relation to Internal Medicine  
Clyde A Clapp
- 2 45-3 00 Fundus Changes in Leukemia  
Leo J Goldbach
- 3 00-4 00 Inspection of Building
- 

L      JOHNS HOPKINS UNIVERSITY SCHOOL OF MEDICINE

Institute of the History of Medicine

Welch Medical Library

Building No 24, Third Floor

(Capacity—100)

(Same program repeated on Thursday)

- 2 00-4 00 The Program will be devoted to the general field of the History of Medicine  
and the Use of a Medical Library
- 4 00-5 00 Visit to the Welch Medical Library
- 

M      JOHNS HOPKINS UNIVERSITY SCHOOL OF HYGIENE

(Wolfe & Monument Sts )

Building No 26

(Also Building No 23 vide infra)

- \*M-I Department of Chemical Hygiene  
Building 26, Lecture Hall, First Floor  
(Capacity—300)  
2 00-3 00 Resumé of results of modern studies on nutrition in this country and  
abroad (First Lecture)  
E V McCollum
- \*M-II Department of Physiology  
Building 26, Seventh Floor  
(Capacity—50)  
3 00-5 00 Hemophilia  
Wm H Howell  
Ultra-violet Light in Relation to the "Common Cold"  
Janet H Clark
- \*M-III Department of Biology  
Building 23, Fourth Floor  
(Capacity—50)  
3 00-5 00 Exhibit and demonstration in human genetics and the constitutional  
factor in disease, with photographs, records from charts, and ap-  
paratus  
Raymond Pearl and W. T Howard, Jr
- \*M-IV Departments of Protozoology, Helminthology and Entomology  
Building 26, Fourth Floor  
(Capacity—50)  
3 00-5 00 Combined demonstration of animal parasites and their vectors.  
R W Hegner, W W Cort and F M Root

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\*(Separate tickets required for each division)

- N**                    **UNIVERSITY OF MARYLAND SCHOOL OF MEDICINE**  
Administration Building  
(Lombard and Greene Streets)  
Chemical Amphitheatre  
(Capacity—250)
- 2 00-2 45 Clinical Pathological Conference Syphilitic Cardio-vascular Disease  
Wm W Love, Jr and C G Warner
- 2 45-3 15 Experimental Focal Infection with Associated Cardiac Pathology  
Noble W Jones, Portland, Ore
- 3 15-4 00 Medical-surgical Conference Pericarditis  
M C Pincoffs and A M Shipley
- 4 00-4 30 Certain Blood-pressure Phenomena in Coronary Artery Disease  
T N Carey
- 

- O**                    **UNIVERSITY OF MARYLAND SCHOOL OF MEDICINE**  
University Hospital  
(Lombard and Greene Streets)  
Surgical Amphitheatre—Fourth Floor  
(Capacity—90)
- 2 00-2 45 Medical Clinic  
O H Perry Pepper, Philadelphia
- 2 45-3 30 Medical Clinic  
Gordon Wilson
- 3 30-4 15 Medical Clinic  
Paul Clough
- 4 15-5 00 Demonstration of Air-conditioning Rooms  
C Gill and S Helms
- 

- P**                    **UNIVERSITY OF MARYLAND SCHOOL OF MEDICINE**  
(Lombard and Greene Streets)  
Pre-clinical Departments  
(No Program on Tuesday)
- 

- Q**                    **UNIVERSITY OF MARYLAND SCHOOL OF MEDICINE**  
Church Laboratory Building  
(Lombard and Greene Streets)  
(No Program on Tuesday)
- 

- R**                    **UNIVERSITY OF MARYLAND SCHOOL OF MEDICINE**  
Mercy Hospital  
College Building  
Saratoga and Calvert Streets  
Saratoga St. entrance, Amphitheatre Second Floor  
(Capacity—120)
- 2 00-2 45 Medical Clinic  
John H Musser, New Orleans
- 2 45-3 30 Endocrine Clinic.  
Harvey G Beck
- 3 30 4 15 Clinic on Rheumatic Pericarditis  
Edgar B Friedenwald

S

SINAI HOSPITAL,  
(Monument and Rutland Streets)  
Lecture Room—Seventh Floor  
(No Program on Tuesday)

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T

BALTIMORE CITY HOSPITALS  
Bay View  
(4940 Eastern Avenue)  
(No Program on Tuesday)

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U

UNION MEMORIAL HOSPITAL  
(33rd and Calvert Streets)  
Nurses Auditorium  
(No Program on Tuesday)

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V

HOWARD A KELLY HOSPITAL  
1418 Eutaw Place  
(Capacity—35)

- 2 00-3 00 Demonstration of apparatus and general discussion of methods of radiation  
Fred West and Curtis F Burnam  
3 00-3 45 Radiation in Gynecology from the Viewpoint of the Internist  
Howard A Kelly  
3 45-4 30 Radiation in Nose and Throat Conditions from the Viewpoint of the Internist  
William Neill and Curtis F Burnam
- 

W

THE CHILDREN'S HOSPITAL SCHOOL  
(Green Spring Avenue and 41st Street)  
(Capacity—25)

- 2 30-3 15 The Production of Sterilized Maggots from the Blue-bottle Fly  
Elizabeth Engle  
3 15-4 00 The Treatment of Chronic Osteomyelitis by Means of Maggots  
Wm S Baer  
4 00-4 30 The Treatment of Arthritis Deformans with Special Reference to Still's Disease  
Wm S Baer and Elizabeth Engle
- 

X

ST AGNES HOSPITAL  
(Caton Avenue near Wilkens Avenue)  
(Capacity—50)

- 2 30-4 30 Symposium on the early clinical diagnosis of cancer, and other features of the cancer problem  
Joseph C Bloodgood and Members of the Hospital Staff
- 

Y

THE SHEPPARD AND ENOCH PRATT HOSPITAL  
(York Road near Towson)  
The Reception Building  
(Capacity—150)

- 2 30-2 45 Introductory Remarks  
Ross McC. Chapman  
2 45-3 15 Notes on Medical Histories of Some Mental Patients  
Lewis B Bliss

- 3 15-4 00 Physical Signs and Symptoms Presenting in the Syndrome of Incipient Schizophrenia  
Harry S Sullivan
- 4 00-4 30 Some Psychological Considerations in the Practice of Medicine  
William V Silverberg

Wednesday, March 25, 1931

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A           JOHNS HOPKINS UNIVERSITY SCHOOL OF MEDICINE  
                  Physiology Building No 25  
                  (Washington and Monument Streets)  
                  Lecture Room—Second Floor  
                  (Capacity—90)

Programs from the Departments of Pharmacology, Physiology and Physiological Chemistry, School of Medicine (Program repeated on Friday)

- 2 00-2 30 Insulin and Other Hormones  
J J Abel
- 2 30-3 00 Use of the Method of Comparative Physiology in Studying Renal Function  
E K Marshall, Jr
- 3 00-3 30 The Interrelationship Between Insulin and the Pituitary Secretions  
E M K Geiling
- 3 30-4 00 The Development of Indicators by Means of which the Reducing Ability of Living Cells may be Studied  
W Mansfield Clark
- 4 00-5 00 Visit to Laboratories of Departments of Pharmacology, Physiology and Physiological Chemistry  
Demonstrations by W Mansfield Clark and Barnett Cohen
- 

B                           JOHNS HOPKINS HOSPITAL  
                                Department of Pathology  
                                Building No 13, Ground Floor, Conference Room  
                                (Capacity—200)

- 2 00-3 00 Clinical Pathological Conference.  
W S Thayer and W G MacCallum
- 3 00-3 30 Studies in Immunity  
A R Rich
- 3 30-4 00 Experimental Nephritis  
S S Blackman
- 

C                           JOHNS HOPKINS HOSPITAL  
                                Department of Medicine  
                                Building No 15, Medical Amphitheatre, 1st Floor  
                                (Capacity—170)

- 2 00-2 45 Clinic  
John H Muster, New Orleans
- 2 45-3 30 Clinic  
L F Barker
- 3 30-4 15 Clinic  
E F Carter

D

## JOHNS HOPKINS HOSPITAL

Department of Medicine

Building No 11, Osler Clinic

(Capacity—25 to each ward)

\*Ward Rounds

- \*D-I Ward I —2 00-3 00 G. A Harrop  
                                   3 00-4 00 P W Clough  
 \*D-II Ward II —2 00-3 00 W. T Longcope  
                                   3 00-4 00 L V Hamman  
 \*D-III Ward III—2 00-3 00 L F. Barker  
                                   3 00-4 00 F. R Ford
- 

E

## JOHNS HOPKINS HOSPITAL

Department of Medicine

Out-Patient Division

Building No 14, Third Floor, Room No 302

(Capacity—90)

- 2 00-2 20 The Diagnosis of Gastro-Intestinal Diseases  
                                   T R Brown  
 2 20-2 40 The Effect of Varying Types of Gastric Resection on the Secretory Function  
                                   E H Gaither and W F Rienhoff, Jr  
 2 40-3 00 Oesophagoscopy and Gastroscopy in Diagnosis  
                                   E B Freeman  
 3 00-3 .20 Bacteriology and Parasitology of the Human Intestine Practical Considera-  
                                   tions  
                                   M Paulson  
 3 20-3 40 Laboratory Studies on Acne Vulgaris  
                                   L W Ketron  
 3 40-4 00 Tuberculosis of the Skin  
                                   L Ginsberg  
 4 00-4 20 Allergic Manifestations of the Ringworm Infections  
                                   J E Kemp  
 4 20-4 40 Pemphigus  
                                   I R Pels
- 

F

## JOHNS HOPKINS HOSPITAL

Department of Medicine

Division of Laboratories

Building No 15, First Floor, Room No 9

(Capacity—60)

(Same program repeated on Friday)

- 2 00-2 20 The Clinical Significance of the Electrocardiogram  
                                   E P Carter  
 2 20-2 40 Heart Failure in Hyperthyroidism  
                                   E C Andrus  
 2 40-3 00 Myocardial Changes in Hyperthyroidism  
                                   D McEachern  
 3 00-3 .20 Syphilitic Aortitis  
                                   B M Baker
- 

\*(Separate tickets for each of these three rounds )

- 3 20-3 40 Skin Reactions in Pneumonia  
W S Tillett
- 3 40-4 00 Pathogenesis of Acute Nephritis  
W T Longcope and N McLeod
- 4 00-5 00 Informal Conferences and Demonstrations in the Cardiographic Laboratory,  
5th Floor, Room 506, and in the Biological Laboratory, 6th Floor,  
Rooms 606, 618
- 

*G*                               JOHNS HOPKINS HOSPITAL  
                                  Department of Obstetrics  
                                  Building No 12, Woman's Clinic, Ground Floor  
                                  (No Program on Wednesday)

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*H*                               JOHNS HOPKINS HOSPITAL  
                                  Department of Pediatrics  
                                  Building No 18, Harriet Lane Home  
                                  (Capacity—100)

- 2 00-2 45 Clinic  
                                  J C Gittings
- 2 45-3 15 The Treatment of Anemias of Infancy with Copper and Iron  
                                  H W Josephs
- 3 15-3 45 The Modern Treatment of Epilepsy  
                                  E M Bridge
- 3 45-4 15 Case Presentations
- 4 15-5 00 Visits to Wards, Dispensary and Laboratories of Harriet Lane Home
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*I*                               JOHNS HOPKINS HOSPITAL  
                                  Department of Psychiatry  
                                  Phipps Psychiatric Institute  
                                  Building No 19, 2nd Floor  
                                  (Capacity—100)

- 2 00-2 20 Principles in Choice and Treatment in House Cases  
                                  A Meyer
- 2 20-2 40 Out-Patient Practice  
                                  E L Richards
- 2 40-3 00 Experimentally Induced Neuroses in Dogs  
                                  W H Gantt
- 3 00-3 20 Somatic Disorders of Functional Origin  
                                  S Katzenelbogen
- 3 20-4 00 Psycholepsy  
                                  W S Muncie
- 

*J*                               JOHNS HOPKINS HOSPITAL  
                                  Department of Surgery  
                                  Building No 14, Seventh Floor, Room 722  
                                  (Capacity—150)

- 2 00-3 00 Arteriovenous Aneurysms  
                                  Dean Lewis
- 3 00-3 30 X-ray Burns and their Treatment  
                                  J Stage Davis



- 3 30-4 00 Several Unusual Cases of Spinal Disease  
R W. Johnson, Jr
- 4 00-4 30 Diagnosis and Treatment of Tic Douleureux and Menière's Disease  
W. Dandy.
- 4 30-5 00 Intestinal Obstruction  
H B Stone
- 

K  
JOHNS HOPKINS HOSPITAL  
Department of Ophthalmology  
Wilmer Ophthalmological Institute.  
Building No 16  
(No Program on Wednesday)

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L  
JOHNS HOPKINS UNIVERSITY SCHOOL OF MEDICINE  
Institute of the History of Medicine  
Welch Medical Library  
(Wolfe and Monument Streets)  
Building No 24, Third Floor  
(No Program on Wednesday)

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M  
JOHNS HOPKINS UNIVERSITY SCHOOL OF HYGIENE  
(Wolfe & Monument Sts)  
Building No 26  
(Also Building No 23 vide infra)

- \*M-I Department of Chemical Hygiene  
Building 26, Lecture Hall, First Floor  
(Capacity—300)  
2 00-3 00 Resumé of results of modern studies on nutrition in this country and abroad (Second Lecture).  
E V McCollum
- \*M-II Department of Biology  
Building 23, Fourth Floor  
(Capacity—50)  
3 00-5 00 Exhibit and demonstration in human genetics and the constitutional factor in disease, with photographs, records from charts, and apparatus  
Raymond Pearl and W T Howard, Jr
- \*M-III Department of Filtrable Viruses  
Building 26, Ninth Floor  
(Capacity—25)  
3 00-5 00 The formation of inclusion bodies in virus III of rabbits, discussion and demonstration with lantern slides  
Roscoe R Hyde
- \*M-IV Departments of Protozoology, Helminthology and Entomology  
Building 26, Fourth Floor  
(Capacity—50)  
3.00-5 00 Combined demonstration of animal parasites and their vectors  
R. W Hegner, W. W. Cort and F M Root

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\*(Separate tickets required for each division)

**N UNIVERSITY OF MARYLAND SCHOOL OF MEDICINE**  
 Administration Building  
 (Lombard and Greene Streets)  
 Chemical Amphitheatre  
 (Capacity—250)

- 2 00-2 45 Clinical Pathological Conference Fat Embolism  
 C Lockard and R B Wright  
 2.45-3 30 Clinic on Disturbances of Motility  
 I J Spear  
 3 30-3 50 Anatomical Aspects of Apoplexy  
 L Freedom  
 3 50-4 10 Clinical Types of Apoplexy  
 A C Gillis  
 4 10-4 30 Surgical Aspects of Apoplexy  
 C Bagley
- 

**O UNIVERSITY OF MARYLAND SCHOOL OF MEDICINE**  
 University Hospital  
 (Lombard and Greene Streets)  
 Surgical Amphitheatre—Fourth Floor  
 (Capacity—90)

- 2 00-2 45 Medical Clinic Pulmonary Tuberculosis  
 L J Moorman, Oklahoma City  
 2 45-3 30 Medical Clinic  
 M C Pincoffs  
 3 30-4 15 Medical Clinic  
 H M Stem  
 4 15-5 00 Demonstration of Air-conditioning Rooms  
 C Gill and S Helms
- 

**P UNIVERSITY OF MARYLAND SCHOOL OF MEDICINE**  
 (Lombard and Greene Streets)  
 Pre-clinical Departments  
 (Capacity—25)

- \*P-I Department of Anatomy, Division of Histology, Embryology and Neural Anatomy Pathology Building, Second Floor  
 2 00-5 00 Demonstration of experimental work on the nature of lung alveoli  
 C L Davis and J L Lutz  
 Demonstration of original laboratory apparatus  
 C L Davis and O G Harne  
 \*P-II Department of Anatomy, Division of Gross Anatomy  
 Administration Building, Museum Laboratory  
 2 00-5 00 Demonstrations  
 (a) Activation of the thyroid by the anterior lobe hormone in man and rat  
 S S Schwartzback, E Uhlenhuth and H W Frenkel  
 (b) Activation of the human thyroid by the anterior lobe hormone in man  
 A V. Dreckwall, T B Ascock and E Uhlenhuth

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\*(Separate tickets required for each division)

(c) The blood circulation of the endocrines demonstrated by the injection method

F M Figge.

(d) Human dissections demonstrating the anatomic innervation of the veins

M A Teitelbaum and E Euhlenhuth

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Q UNIVERSITY OF MARYLAND SCHOOL OF MEDICINE

Church Laboratory Building  
(Lombard and Greene Streets)  
(No Program on Wednesday)

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R UNIVERSITY OF MARYLAND SCHOOL OF MEDICINE

Mercy Hospital  
College Building  
(Saratoga and Calvert Streets)  
Saratoga St entrance, Amphitheatre, Second Floor  
(Capacity—120)

2 00-2 40 Clinical Pathological Conference Coronary Thrombosis  
C C W Judd and Standish McCleary

2 40-3 10 The Appendicitis Problem  
Alexius McGlannan

3 10-3 40 Brain Abscess  
Charles Bagley, Jr

3 40-4 00 Purulent Perimenigitis  
D J Pessagno

4 00-4 15 Discussion of a Case of Sino-auricular Block  
T C Wolfe

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S SINAI HOSPITAL

(Monument and Rutland Streets)  
Lecture Room—Seventh Floor  
(Capacity—75)

2 00-2 40 Medical Clinic  
James S McLester, Birmingham

2 40-3 20 Medical Clinic  
Charles R Austrian

3 20-3 40 Spontaneous Hemorrhage into the Adrenals of the Newborn—Report of a Case  
John A Askin

3 40-4 00 Congenital Abnormalities  
A J Schaffer

4 00-4 20 An Unusual Case of Bichloride of Mercury Poisoning  
Jos E Gichner

4:20-4 20 Narcolepsy—A Case Report  
J S Guttmacher.

4 20-5 00 Case of Thallium Poisoning  
M Sherry

T

## BALTIMORE CITY HOSPITALS

Bay View

(4940 Eastern Avenue)

\*T-I

Ward A

(Capacity—30)

2 30-4 30 Medical Clinic and Ward Rounds

Thomas R Boggs and Staff

\*T-II

Tuberculosis Hospital

(Capacity—25)

2 30-4 30 Diagnostic and Therapeutic Ward Rounds

C C Habliston, T B Aycock and Staff

U

## UNION MEMORIAL HOSPITAL

(33rd and Calvert Streets)

Nurses Auditorium

(Capacity—200)

2 00-2 45 The Diagnosis of Traumatic and Suppurative Cerebral Diseases from the  
Standpoint of the Physician

Wells P Eagleton

2 45-3 15 Remarks on Peptic Ulcer

J M T Finney

3 15-3 40 Denervation of the Ureter A Clinical and Anatomical Study Report of  
Cases Lantern Slides

L R Wharton

3 40-4 00 The Treatment of Angina Agranulocytica

L P Hamburger and C A Waters

4 00-4 20 Avertin Anaesthesia

J Arthur York

4 20-4 40 The Medical Aspects of Choroiditis

Cecil Bagley

V

## HOWARD A KELLY HOSPITAL

(1418 Eutaw Place)

(No Program on Wednesday)

W

## THE CHILDREN'S HOSPITAL SCHOOL

(Green Spring Avenue and 41st Street)

(No Program on Wednesday)

X

## ST AGNES HOSPITAL

(Caton Avenue near Wilkens Avenue)

(No Program on Wednesday)

Y

## THE SHEPPARD AND ENOCH PRATT HOSPITAL

(York Road near Towson)

(The Reception Building)

(No Program on Wednesday)

Thursday, March 26 1931

\*(Separate Tickets required for each division)

Thursday, March 26, 1931

## A      JOHNS HOPKINS UNIVERSITY SCHOOL OF MEDICINE

Physiology Building No 25  
 (Washington and Monument Streets)  
 Lecture Room—Second Floor  
 (Capacity—90)

Program from the Department of Anatomy of the Medical School and the Department of Embryology of the Carnegie Institution of Washington (Same program as on Tuesday).

2 00-2 20 Endocrines and Reproduction

C G Hartmann

2.20-2 40 Development of the Mammalian Egg

G L Streeter

2 40-3 00 Behavior of Living Cells (Motion Pictures)

W H Lewis

3 00-3 30 Human Growth and Human Evolution

A H Schultz

3 30-5 00 Visit to the Laboratories of the Department of Anatomy (Building No. 22),  
 and the Carnegie Institution, Department of Embryology (Building  
 No 23, Second Floor)

## B      JOHNS HOPKINS HOSPITAL

Department of Pathology  
 Building No 13, Ground Floor, Conference Room  
 (No Program on Thursday)

## C      JOHNS HOPKINS HOSPITAL

Department of Medicine  
 Building No 15, Medical Amphitheatre, 1st Floor  
 (Capacity—170)

2 00-2 45 Clinic

O H Perry Pepper, Philadelphia

2 45-3 30 Clinic

L F Barker

3 30-4 15 Medical-surgical Conference

C R Austrian and R T Miller

Thursday, March 26, 1931 (Continued)

## D      JOHNS HOPKINS HOSPITAL

Department of Medicine  
 Building No 11, Osler Clinic  
 (Capacity—25 to each ward)

\*Ward Rounds

\*D-I Ward I —2 00-3 00 T R Boggs

3.00-4 00 H M Thomas

\*D-II Ward II —2 00-3 00 W T Longcope

3.00-4 00 G A Harrop

\*D-III Ward III—2 00-3 00 J T King, Jr

3 00-4 00 T. R Brown

Isolation—2 00-3 00 P H Long.

3 00-4 00 W. S. Tillett

\*-(Separate tickets for each of these rounds)

E

## JOHNS HOPKINS HOSPITAL

Department of Medicine

Out-Patient Division

Building No 14, Third Floor, Room No 302

(Capacity—90)

- 2 00-3 30 Program from Protein Sensitization Clinic  
 2 00-2 30 General Considerations  
     L N Gay  
 2 30-3 00 Presentation of Cases  
     L N Gay, N B Herman and T F Daniels  
 3 00-3 30 Technique in Diagnosis  
     L N Gay, N B Herman and T F Daniels  
 3 30-5 00 Program from Diabetic Clinic  
 3 30-4 00 Management of Ambulatory Diabetes Mellitus  
     E. J Leopold  
 4 00-4 30 Changes in Blood Sugar Curves  
     M I Gichner  
 4 30-5 00 Diabetes Mellitus Complicated with Pregnancy  
     Albert Weinstein

F

## JOHNS HOPKINS HOSPITAL

Department of Medicine

Division of Laboratories

Building No 15, First Floor, Room No 9

(Capacity—60)

(Same program as on Tuesday)

- 2 00-2 20 Sulphaemoglobinaemia  
     G A Harrop  
 2 20-2 40 A Liver Function Test with Bilirubin  
     G A Harrop  
 2 40-3 00 Present Day Conceptions of Immunity in Syphilis  
     A M Chesney  
 3 00-3 20 Role of Trauma in the Localization of Syphilitic Lesions  
     T. B Turner  
 3 20-3 40 Specificity of the Diagnostic Tests for Syphilis  
     Harry S Eagle  
 4 00-5 00 Informal Conferences and Demonstrations in Chemical Laboratory of Medical  
     Clinic, 5th Floor, Room 516, and in Laboratory of Experimental Syphilis  
     6th Floor, Room 601

G

## JOHNS HOPKINS HOSPITAL

Department of Obstetrics

Building No 12, Woman's Clinic, Ground Floor

(Capacity—72)

(Same program as on Tuesday)

- 2 00-2 20 Medical Indications for Sterilization  
     J W Williams  
 2 20-2 40 1st Results of Chronic Nephritis Complicated by Pregnancy  
     H. J Stander

- 2 40-3 00 Diabetes and Pregnancy  
C. H. Peckham.
- 3.00-3 20 Blood and Urinary Protein in the Toxemias of Pregnancy  
M J Eastman
- 3:20-3 40 Heart Disease and Pregnancy  
A F. Guttmacher
- 3'40-4 00 The Pituitary Gland and the Internal Genitalia.  
I Hofbauer
- 4 00-5 00 Informal Conferences in the Laboratories of the Department of Obstetrics  
4th and 5th Floors, Woman's Clinic
- 

*H*

JOHNS HOPKINS HOSPITAL  
Department of Pediatrics  
Building No 18, Harriet Lane Home  
(Capacity—100)

- 2 00-2 45 Clinic on Bone Disorders  
E A Park
- 2 45-3 05 The Cause of Acidosis Associated with Diarrhea  
L. E. Holt, Jr
- 3 05-3 25 The Treatment of Anemias of Infancy with Copper and Iron  
H W. Josephs
- 3 25-3 40 An Unusual Case of Bone Dystrophy  
L. Kajdi
- 3 40-4 00 Observations on the Factors Influencing the Toxicity of Ergosterol  
D H Shelling
- 4 00-4 15 Demonstration of Calcification in Vitro  
P G Shipley
- 4 15-5 00 Visits to Wards, Dispensary and Laboratories of Harriet Lane Home
- 

*I*

JOHNS HOPKINS HOSPITAL  
Department of Psychiatry  
Phipps Psychiatric Institute  
Building No 19, 2nd Floor  
(No Program on Thursday)

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*J*

JOHNS HOPKINS HOSPITAL  
Department of Surgery  
Building No 14, Seventh Floor, Room 722  
(Capacity—150)

- 2 00-2 30 Clinic on the Diagnosis and Treatment of Hyperthyroidism  
H M Thomas and W. F. Rienhoff, Jr
- 2 30-3 00 Pre-operative and Post-operative Treatment of Prostatic Obstruction  
H H Young.
- 3 00-3 30 Medical Aspects of Prostatic Obstruction  
E C Andrus
- 3 30-3 45 Presentation of Cases of Congenital Urinary Obstruction in Childhood  
W A Frontz
- 3 45-4 00 Intravenous Therapy in the Treatment of Infections of the Genito-Urinary Tract  
J A C. Colston

K

JOHNS HOPKINS HOSPITAL  
Department of Ophthalmology  
Wilmer Ophthalmological Institute  
Building No 16  
(Capacity—110)

- 2 00-2 15 Color Fields as an Aid in the Diagnosis of Intracranial Lesions  
A L MacLean  
2 15-2 30 Ocular Findings in Trichinosis  
Cecil Bagley  
2 30-2 45 The Character of Diabetic and Renal Exudates in the Retina  
Benjamin Rones  
2 45-3 00 Clinical Significance of Choroidal Tubercles  
R T Paton.  
3 00-4 00 Inspection of Building
- 

L

JOHNS HOPKINS UNIVERSITY SCHOOL OF MEDICINE  
Institute of the History of Medicine  
Welch Medical Library  
(Wolfe and Monument Streets)  
Building No 24, Third Floor  
(Capacity—100)  
(Same program as on Tuesday)

- 2 00-4 00 The Program will be devoted to the general field of the History of Medicine  
and the Use of a Medical Library  
4 00-5 00 Visit to the Welch Medical Library
- 

M

JOHNS HOPKINS UNIVERSITY SCHOOL OF HYGIENE  
(Wolfe and Monument Sts)  
Building No 26  
(Also Building No 23 vide infra)

- \*M-I Department of Chemical Hygiene  
Building 26, Lecture Hall, First Floor  
(Capacity—300)  
2 00-3 00 Resume of results of modern studies on nutrition in this country  
and abroad (Third Lecture).  
E V McCollum  
\*M-II Department of Biostatistics  
Building 26, Third Floor  
(Capacity—50)  
3 00-5 00 Statistics in Medicine (15 minutes), and special topics "The Number  
of Typhoid-carriers in New York City" and "Measles Epidemics in  
Baltimore in a 28-year Period"  
S J Reed  
\*M-III Department of Biology  
Building 23, Fourth Floor  
(Capacity—50)  
3 00-5 00 Exhibit and demonstration in human genetics and the environmental  
factor in disease with photographic records from elms and asparagus.  
Raymond Pearl and W T Howard Jr

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\* (Separate tickets required for each day's work)



- \*M-IV Department of Protozoology, Helminthology and Entomology  
 Building 26, Fourth Floor  
 (Capacity—50)  
 3 00-5.00 Combined demonstration of animal parasites and their vectors  
 R W Hegner, W W Cort and F. M Root
- 

- N UNIVERSITY OF MARYLAND SCHOOL OF MEDICINE  
 Administration Building  
 (Lombard and Greene Streets)  
 Chemical Amphitheatre  
 (Capacity—250)
- 2 00-2 45 Clinical Pathological Conference Thyroiditis and Riedel's Struma  
 A M. Shipley and H R Spencer
- 2 45-3 30 Clinic on Diabetes  
 V Virgil Simpson, Louisville
- 3 30-3 50 Some Studies in the Physiology of Bile  
 F A Ries
- 3 50-4 10 Diagnosis in Biliary Tract Disease  
 H M. Stein
- 4 10-4 30 Present Status of the Sedimentation Test  
 J G Huck.
- Thursday, March 26, 1931 (Continued)
- 

- O UNIVERSITY OF MARYLAND SCHOOL OF MEDICINE  
 University Hospital  
 (Lombard and Greene Streets)  
 Surgical Amphitheatre—Fourth Floor  
 (Capacity—90)
- 2 00-2 45 Medical Clinic Diabetes  
 John R. Williams, Rochester N Y
- 2 45-3 30 Medical Clinic Hypertension  
 W A Baetjer
- 3 30-4 15 Medical Clinic.  
 C C. Habliston
- 4.15-5 00 Demonstration of Air-conditioning Rooms  
 C Gill and S Helms
- 

- P UNIVERSITY OF MARYLAND SCHOOL OF MEDICINE  
 (Lombard and Greene Streets)  
 Pre-clinical Departments  
 (No Program on Thursday)
- 

- Q UNIVERSITY OF MARYLAND SCHOOL OF MEDICINE  
 Church Laboratory Building  
 (Lombard and Greene Streets)  
 (No Program on Thursday)

R UNIVERSITY OF MARYLAND SCHOOL OF MEDICINE  
 Mercy Hospital  
 College Building  
 (Saratoga and Calvert Streets)  
 Saratoga St entrance, Amphitheatre, Second Floor  
 (Capacity—120)

2 00-2 45 Clinic on Sickle-cell Anemia  
 V. P. Sydenstricker, Augusta  
 2 45-3 30 Neurological Clinic  
 A C Gillis  
 3 30-4 15 Medical-surgical Conference on Cases of Hemolytic Jaundice  
 H R Peters and W D Wise

S SINAI HOSPITAL  
 (Monument and Rutland Streets)  
 Lecture Room—Seventh Floor  
 (No Program on Thursday)

T BALTIMORE CITY HOSPITALS  
 Bay View  
 (4940 Eastern Avenue)  
 (No Program on Thursday)

U UNION MEMORIAL HOSPITAL  
 (33rd and Calvert Streets)  
 Nurses Auditorium  
 (No Program on Thursday)

V HOWARD A KELLY HOSPITAL  
 (1418 Eutaw Place)  
 (Capacity—35)

2 00-2 30 Radiation in Urology  
 William Neill  
 2 30-3 00 Hodgkin's Disease  
 Curtis F. Burnam  
 3 00-3 45 Radiation in Skin Diseases  
 Edmund Kelly  
 3 45-4 30 Radiation in Eye Conditions  
 William Neill, Jr.

W THE CHILDREN'S HOSPITAL SCHOOL  
 (Green Spring Avenue and 41st Street)  
 (No Program on Thursday)

X ST AGNES HOSPITAL  
 (Caton Avenue near Wilkens Avenue)  
 (No Program on Thursday)

Y THE SHEPPARD AND ENOCH PRATT HOSPITAL  
(York Road near Towson)  
The Reception Building  
(Capacity—150)

- 2 30-3 00 Case Presentations  
Eleanor B Saunders.  
3 00-3 30 Case Presentations  
Harry M Murdock  
3 30-4 00 Case Presentations  
Niels L Anthonisen  
4 00-4 .30 Case Presentations  
Alexander R Martin.

Friday, March 27, 1931

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A JOHNS HOPKINS UNIVERSITY SCHOOL OF MEDICINE  
Physiology Building No 25  
(Washington and Monument Streets)  
Lecture Room—Second Floor  
(Capacity—90)

Program from the Departments of Pharmacology, Physiology and Physiological Chemistry, School of Medicine (Same program as on Wednesday).

- 2.00-2 30 Insulin and Other Hormones  
J J. Abel  
2 30-3 00 Use of the Method of Comparative Physiology in Studying Renal Function  
E K Marshall, Jr  
3 00-3 30 The Interrelationship Between Insulin and the Pituitary Secretions.  
E M K. Geiling  
3 30-4 00 The Development of Indicators by Means of which the Reducing Ability of Living Cells may be Studied  
W Mansfield Clark  
4 00-5 00 Visit to Laboratories of Departments of Pharmacology, Physiology and Physiological Chemistry  
Demonstrations by W Mansfield Clark and Barnett Cohen
- 

B JOHNS HOPKINS HOSPITAL  
Department of Pathology  
Building No 13, Ground Floor, Conference Room  
(Capacity—200)

- 2 00-3 00 Clinical Pathological Conference  
W S Thayer and W G MacCallum  
3 00-3 10 Studies in Immunity.  
A R. Rich  
3 10-4 00 Experimental Nephritis  
S S Blackman

C

## JOHNS HOPKINS HOSPITAL

Department of Medicine

Building No 15, Medical Amphitheatre, 1st Floor  
(Capacity—170)

- 2 00-2 45 Clinic  
James S McLester, Birmingham
- 2 45-3 30 Clinic  
W T Longcope
- 3 30-4 15 Clinic  
C R Austrian
- 

D

## JOHNS HOPKINS HOSPITAL

Department of Medicine

Building No 11, Osler Clinic  
(Capacity—25 to each ward)

\*Ward Rounds

- \*D-I Ward I 2 00-3 00 W S Thayer  
3 00-4 00 T. P Sprunt
- \*D-II Ward II 2 00-3 00 P W Clough  
3 00-4 00 J T King, Jr
- \*D-III Ward III 2 00-3 00 E P Carter  
3 00-4 00 E C Andrus
- 

E

## JOHNS HOPKINS HOSPITAL

Department of Medicine

Out-Patient Division

Building No 14, Third Floor, Room No 302  
(Capacity—90)

- 2 00-2 30 The Treatment of Diseases of the Gastro-Intestinal Tract  
T R Brown
- 2 30-3 00 Non-Specific Protein Therapy in Diseases of the Digestive Tract  
Lay Martin
- 3 00-3 30 Newer Aspects of some Organic Intestinal Disorders  
M Paulson
- 3 30-4 00 Diagnosis and Treatment of Cardiospasm and Cancer of the Oesophagus  
E B Freeman and H E Wright
- 4 00-5 00 X-Ray Conference  
F H Baetjer and B M Baker
- 

F

## JOHNS HOPKINS HOSPITAL

Department of Medicine

Division of Laboratories

Building No 15, First Floor, Room No 9  
(Capacity—60)

(Same program as on Wednesday)

- 2 00-2 20 The Clinical Significance of the Electrocardiogram  
E P Carter
- 2 20-2 40 Heart Failure in Hyperthyroidism  
E C Andrus

\*(Separate tickets for each of these three lectures)

- 2 40-3 00 Myocardial Changes in Hyperthyroidism  
D McEachern
- 3 00-3 20 Syphilitic Arthritis  
B. M. Baker
- 3 20-3 40 Skin Reactions in Pneumonia  
W. S. Tillett.
- 3 40-4 00 Pathogenesis of Acute Nephritis  
W. T. Longcope and N. McLeod
- 4 00-5 00 Informal Conferences and Demonstrations in the Cardiographic Laboratory,  
5th Floor, Room 506, and in the Biological Laboratory, 6th Floor, Rooms  
606, 618
- 

## G

## JOHNS HOPKINS HOSPITAL

Department of Obstetrics  
Building No 12, Woman's Clinic, Ground Floor  
(No Program on Friday)

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## H

## JOHNS HOPKINS HOSPITAL

Department of Pediatrics  
Building No 18, Harriet Lane Home  
(No Program on Friday)

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## I

## JOHNS HOPKINS HOSPITAL

Department of Psychiatry  
Phipps Psychiatric Institute  
Building No 19, 2nd Floor  
(Capacity—100)

- 2 00-2 20 Experimental Diabetes Insipidus  
C P Richter
- 2 20 2 40 Bromide Therapy  
O Diethelm
- 2 40-3 00 The Significance of Meningeal Permeability  
S Katzenelbogen
- 3 00-3 20 Suicide Problems  
Ruth E Fairbank
- 3 20-3 40 The Role of the Central Nervous System in the Action of the Metabolism  
Raising Principle of the Thyroid Gland  
H G Wolff
- 3 40-4 00 A Comparison of the Use of Stramonium and Hyoscine in Postencephalitic  
Parkinson Syndrome  
L Hohman
- 4 00 Laboratory Demonstration  
C. Bagley.

J

JOHNS HOPKINS HOSPITAL  
Department of Surgery  
Building No 14, Seventh Floor, Room 722  
(Capacity—150)

- 2 00-3 00 Peptic Ulcer Diagnosis and Treatment  
J M T. Finney, Sr  
3 00-3 30 Title to be announced later  
S J Crowe  
3 30-4 00 Diagnosis and Treatment of Retroperitoneal Abscesses  
G Bennett  
4 00-4 30 Responsibility of the Internist in the Early Diagnosis of Renal Stasis  
G L Hunner  
4 30-5 00 Pathological Lesions in the Pelvic Organs in Five Hundred Cases of Myomata Uteri  
L R Wharton
- 

K

JOHNS HOPKINS HOSPITAL  
Department of Ophthalmology  
Wilmer Ophthalmological Institute  
Building No 16  
(No Program on Friday)

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L

JOHNS HOPKINS UNIVERSITY SCHOOL OF MEDICINE  
Institute of the History of Medicine  
Welch Medical Library  
(Wolfe and Monument Streets)  
Building No 24, Third Floor  
(No Program on Friday)

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M

JOHNS HOPKINS UNIVERSITY SCHOOL OF HYGIENE  
(Wolfe and Monument Sts)  
Building No 26  
(Also Building No 23 vide infra)

- \*M-I Department of Chemical Hygiene  
Building 26, Lecture Hall, First Floor  
(Capacity—300)  
2 00-3 00 Resume of results of modern studies on nutrition in this country and abroad (Fourth Lecture).  
E. V. McCollum  
\*M-II Building 26, Eight Floor  
(Capacity—50)  
3 00-5 00 Demonstration of Animal Colony and of Specific Types of Metabolism in Animals  
E. V. McCollum
- 

\*(Separate tickets required for each division)

**\*M-III Department of Bacteriology**

3 00-5 00 Visit to the Laboratory.

W W. Ford

Discussion Control of abortion bacillus infections in dairy cattle.

S R Damon

Building 26, Fifth Floor

(Capacity—25)

Demonstrations

Cultures of anaerobes on aerobic plates

Bettylee Hampil

Bartonella, muris and Eperythrozoon coccoides

C P Eliot

Spirochetes and fusiform bacilli

Minnie B Harris

**\*M-IV Department of Immunology**

3 00-5 00 Visit to Laboratory

G H Bailey

Demonstrations

Cultures of Amoeba histolytica and Amoeba barrata

Electrophoresis of bacteria in relation to virulence

R L Thompson

Antigenic properties of pneumococci

G. H Bailey

**\*M-V Department of Biology**

Building 23, Fourth Floor

(Capacity—50)

3 00-5 00 Exhibit and demonstration in human genetics and the constitutional factor in disease, with photographs, records from charts, and apparatus  
Raymond Pearl and W T Howard, Jr.**\*M-VI Department of Filtrable Viruses**

Building 26, Ninth Floor

(Capacity—25)

3 00-5 00 The formation of inclusion bodies in virus III of rabbits, discussion and demonstration with lantern slides

Roscoe R Hyde

V

**UNIVERSITY OF MARYLAND SCHOOL OF MEDICINE**

Administration Building

(Lombard and Greene Streets)

Chemical Amphitheatre

(Capacity—250)

2 00-2 15 Clinical Pathological Conference Carbon-Monoxide Poisoning

L A M Krause and L Freedom

2 15-3 00 Fatalities in Bronchial Asthma

H. Bubert.

3 00-3 20 Cases of Hemothorax

Joseph E. Gichner.

3 20-3 50 Lung Tumors

C C Habliston

- 3 50-4 10 Results with Different Types of Phrenicotomy  
T. B. Aycock
- 4 10-4 30 Pulmonary Embolism  
C. G. Warner

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O UNIVERSITY OF MARYLAND SCHOOL OF MEDICINE  
University Hospital  
(Lombard and Greene Streets)

Surgical Amphitheatre—Fourth Floor  
(Capacity—90)

- 2 00-2 45 Medical Clinic—Hodgkin's Disease  
E. H. Falconer, San Francisco
- 2 45-3 30 Medical Clinic  
Julius Friedenwald
- 3 30-4 15 Medical Clinic  
Wm. S. Love, Jr.
- 4 15-5 00 Demonstration of Air-conditioning Rooms  
C. Gill and S. Helms

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P UNIVERSITY OF MARYLAND SCHOOL OF MEDICINE  
(Lombard and Greene Streets)

Pre-clinical Departments

- \*P-I Department of Pharmacology  
Gray Laboratory, Second Floor  
(Capacity—50)

- 2 00-5 00 Demonstrations
- (a) Original colorimetric standards for estimating oxidation products (Adrenalin)  
Ruth Musser
  - (b) The action of soporifics and of digitalis glycosides on the heart  
W. H. Schultz and W. E. Evans
  - (c) The action of sex-hormones and a demonstration of the Ashman & Allen pregnancy test  
H. Schroeder and W. L. Schultz
  - (d) Enzyme studies and a demonstration of a colorimetric test  
F. Steigerwaldt
  - (e) Pharmacological studies of nitrous oxide and some other anesthetics  
H. Schroeder

- \*P-II Department of Physiology  
Gray Laboratory, First Floor  
(Capacity—15)

2 00-5 00 Demonstration of A. S. B. and other physiological experiments  
O. G. Horne

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\*(Separate tickets required for each session.)



Q

## UNIVERSITY OF MARYLAND SCHOOL OF MEDICINE

Church Laboratory Building  
(Lombard and Greene Streets)  
Lecture Room—First Floor  
(Capacity—150)

- 2 00-2 45 Cerebral Hemorrhage in the Newborn, (with motion pictures)  
C L Joslin and C Bagley, Jr.
- 2 45-3 30 Clinic on common acquired deformities of the lower extremities in childhood  
and their treatment  
R. W. Johnson, Jr
- 3 30-4 00 Diabetes in Childhood  
H M Stein
- 4 00-4 30 Sinus Disease in Childhood  
E Looper.
- 4 30-5 00 Tuberculosis in Childhood  
A H. Finkelstein
- 

R

## UNIVERSITY OF MARYLAND SCHOOL OF MEDICINE

Mercy Hospital  
College Building  
(Saratoga and Calvert Streets)  
Saratoga St entrance, Amphitheatre, Second Floor  
(Capacity—120)

- 2 00-2 45 Clinical Pathological Conference Psittacosis  
M C Pincoffs and Standish McCleary
- 2 45-3 15 Treatment of Common Poisonings  
H R Peters
- 3 15-3 35 Chyluria  
George McLean
- 3 35-4 00 The Diazo-test in Uremia  
J S Eastland and E G Schmidt
- 4 00-5 00 (Bronchoscopic Clinic, Hospital Building, 5th Floor)  
Bronchoscopic Clinic  
W F. Zinn.
- 

S

SINAI HOSPITAL  
(Monument and Rutland Streets)  
Lecture Room—Seventh Floor)  
(Capacity—75)

- 2 00-2 40 Medical Clinic  
Moses Barron, Minneapolis
- 2 40-3 20 Medical Clinic.  
S Wolman
- 3 20-3 40 Vaccine Treatment of Multiple Sclerosis  
I J Spear and W H Davis
- 3 40-4 00 Case Report  
Edgar Friedenwald
- 4 00 4 20 Skin Lesions Associated with Neisserian Infections  
M. S Rosenthal

- 4 20-4 40 An Unusual Case of Tularemia  
M G Gichner  
4 40-5 00 The Vestibular Form of Encephalitis Lethargica  
S Whitehouse

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**T** BALTIMORE CITY HOSPITALS  
Bay View  
(4940 Eastern Avenue)  
(No Program on Friday)

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- U** UNION MEMORIAL HOSPITAL  
(33rd and Calvert Streets)  
Nurses Auditorium  
(Capacity—200)
- 2 00-2 45 Medical Clinic  
J C Meakins, Montreal  
2 45-3 15 Recent Contributions to Ovarian Physiology  
E H Richardson  
3 15-3 35 End Results of Surgery for Gastro-duodenal Ulcer  
E M Hanrahan, Jr  
3 35-3 55 Chronic Mononucleosis  
T P Sprunt  
3 55-4 15 The Thymus Problem  
D C Wharton Smith  
4 15-4 30 The Normal Structure and Circulation of the Thyroid Gland  
W F Rienhoff, Jr  
4 30-5 00 Nephritis Complicating Pregnancy  
J McF Bergland

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**V** HOWARD A KELLY HOSPITAL  
(1418 Eutaw Place)  
(No Program on Friday)

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**W** THE CHILDREN'S HOSPITAL SCHOOL  
(Green Spring Avenue and 41st Street)  
(No Program on Friday)

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**Y** ST. AGNES HOSPITAL  
(Caton Avenue near Walters Avenue)  
(No Program on Friday)

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**Z** THE SHEPPARD AND ENOCH PRATT HOSPITAL  
(York Road near Totten)  
The George & E. Pratt  
(No Program on Friday)

## College News Notes

BALTIMORE PROGRAM OF ENTERTAINMENT FOR  
VISITING WOMEN*Monday, March 23, 1931*

- Morning Registration at The Alcazar  
 Afternoon Registration at The Alcazar  
 5 30 o'clock Gallery Talk at Museum of Art by Florence H Austrian

*Tuesday, March 24, 1931*

- Afternoon 2 45 o'clock Leave The Alcazar in private motors for drive through Roland Park and Guilford, and a tea given by Mrs Lewellys Barker and Mrs Sydney Miller at the William H Welch Medical Library of the Johns Hopkins University Medical School

*Wednesday, March 25, 1931*

- Morning 11 00 o'clock Walters Art Gallery  
 Afternoon 1 00 o'clock Lunch at the Women's City Club, 15 W Mt Vernon Place, as guests of the local Committee on the Entertainment of Visiting Women  
 2 30 o'clock Sightseeing Tour of Old Baltimore in Gray Line Busses  
 4 15 o'clock Tea at residence of Mr and Mrs Blanchard Randall, 8 W Mt Vernon Place Hostesses Mrs Maurice Pincoffs and Local Committee

*Thursday, March 26, 1931*

- Afternoon. 1 15 o'clock Leave The Alcazar in Gray Line Busses for trip to Annapolis, there to visit the U S Naval Academy and also historic houses, the latter will be described in an illustrated talk given by Prof R T H Halsey in Great Hall of McDowell Hall, St Johns College  
 Evening 7 30 o'clock The Annual Banquet to which women guests are cordially invited. (See general program for details)

*Friday, March 27, 1931*

No special program has been arranged Information regarding sight-seeing trips, shopping, or places for luncheon or other entertainment may at all times be obtained at the Information Desk in The Alcazar

## NOMINATIONS FOR ELECTIVE OFFICERS

1931-32

The Nominating Committee herewith transmits the following nominations for elective officers of the American College of Physicians for the year 1931-32

- President Elect - Francis M Pottenger, Monrovia, Calif  
 1st Vice President - Aldred Scott Warthin, Ann Arbor, Mich  
 2nd Vice President - Charles G Jennings, Detroit Mich  
 3rd Vice President - John A Lichty, Clifton Springs, N Y

January 9, 1931

Respectfully Submitted,  
 Alfred Stengel, *Chairman*  
 J H Means  
 James S McLester  
 E B Bradley

## THE JOHN PHILLIPS MEMORIAL PRIZE

The Committee on the John Phillips Memorial Prize announces that thirty-one theses were received in competition for the 1931 award. These theses were read separately by each of a Committee of five, and, where deemed necessary, were referred to specially selected referees. The final decision of the Committee and referees is that, in accordance with a condition of the original announcement (namely, "The College reserves the right to make no award of the prize if a sufficiently meritorious piece of work has not been received"), no thesis was deemed sufficiently worthy to warrant the bestowal of the prize this year.

The theses are being returned to the authors with the above announcement. A further announcement concerning the award for 1932 will be made within a few weeks.

## COMMITTEE ON FINANCE

In accordance with the resolution adopted at the last meeting of the Board of Regents at Louisville, Ky., on November 11, President Sidney R. Miller has appointed the following Committee on Finance for 1931:

Dr. Clement R. Jones, Chairman, Pittsburgh

Dr. James S. McIester, Birmingham

Dr. Charles F. Martin, Montreal

Dr. Francis M. Pottenger, Monrovia

Dr. Charles G. Jennings, Detroit

Among the responsibilities of the Committee on Finance are examining annual operating statements, security records, proposed budgets, and to carry on such activities as in their judgment will stimulate Life Membership. This Finance Committee is also instructed to formulate a recommendation to the Board of Regents for fixing a term of service for a standing Finance Committee.

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 COMMITTEE ON COLLEGE  
INSIGNIA

taxis, With and Without Hereditary (Familial) Multiple Hemorrhagic Telangiectasia (Osler's Disease),"

Dr Ray W Kissane (Fellow), Columbus, Ohio 3 reprints "Area of the Body Surface and Measurements of the Normal Heart in Children," "Electrocardiographic Electrodes," "Area of the Body Surface and Measurements of the Normal Heart,"

Dr Sinclair Luton (Fellow), St Louis, Mo 2 reprints "The Treatment of Chronic Heart Disease," "Comparison of Methods Used for Estimating the Size of the Heart,"

Dr William D Reid (Fellow), Boston, Mass 1 reprint "The Heart in Pregnancy"

Dr Gerald M Cline (Fellow), Bloomington, Ill, addressed the College Alumni Club of Bloomington, December 19, on "What a Baby Costs"

Dr Linn J Boyd (Fellow), New York and Editor-in-Chief of the Journal of the American Institute of Homeopathy, is the author of an article "Kotschau's Scientific Basis of Homeopathy—a Simplified Version," which appeared in the December number of the Journal of the American Institute of Homeopathy

Dr Curran Pope (Associate), Louisville, was a guest of honor at the meeting of the Cumberland Valley Medical Society, which met at Harlan, Ky, on December 9. Dr Pope addressed the Society upon the newer methods of treatment for Chronic Infections and Toxemias by the Induction of Therapeutic Fever and especially upon localized thermic elevation of the temperature of the liver

Dr S Calvin Smith (Fellow), Philadelphia Vice President of the Philadelphia County Medical Society, broadcast a talk "What can be done for Heart Disease from WJAN on October 11. This talk was published in the Weekly Roster and Medical Digest on December 6

Dr Sidney D Wilson (Fellow) Springfield Ill, addressed the fifteenth annual

meeting of the Indiana Society for Mental Hygiene, December 8, on "Organization of Community Facilities for the Prevention, Care and Treatment of Nervous and Mental Diseases"

Dr Harry Malcome Hedge (Fellow), Chicago, delivered an address on "Treatment of Common Skin Diseases" before the La Porte County Medical Society held at La Porte (Indiana), November 23

Dr Robert M Moore (Fellow), Indianapolis, addressed the Hamilton County (Indiana) Medical Society, November 11, on "Internal Medicine"

Dr George F Pfahler (Fellow), Philadelphia, spoke on "Some Practical Points in the Early Diagnosis of Cancer" at the Seminar of the Philadelphia County Medical Society on Friday, December 12. He was introduced by Dr James M Anders (Master), Philadelphia

Dr Walter C Alvarez (Fellow), Rochester, Minn, recently delivered an address on "Problems of Gastro-Enterology" before the Washtenaw County Medical Society, Ann Arbor

Dr Chester W Waggoner (Fellow), Toledo, addressed the Wayne County Medical Society (Detroit), December 2, on "Chronic Duodenal Stasis"

The Oklahoma City Clinical Society was addressed November 5-7, by Dr Francis M Pottenger (Fellow), Monrovia, Calif, on "Importance of Visceral Neurology in General Medicine"

The following Fellows of the College were speakers at the three-day graduate course on heart disease arranged by the Heart Committee of the San Francisco County Medical Society, December 9-11

Dr William J Kerr (Fellow), San Francisco—"Use of Quinine in Treatment of Cardiac Irregularities,"

Dr Arthur L Bloomfield (Fellow), San Francisco together with several other doctors demonstrated various types of heart disease

Dr L. Napoleon Boston (Fellow), Philadelphia, gave a Health Radio Talk, "Goitre," under the auspices of the Philadelphia County Medical Society, December 16

Dr Hans Lissner (Fellow), San Francisco, recently delivered an address on Clinical Endocrinology before a meeting of the Sacramento Society for Medical Improvement

Dr Mary O'Malley (Fellow), Washington, D C, celebrated the twenty-fifth anniversary of her service at the St Elizabeth's Hospital, and was recently entertained by the medical staff of the hospital. Dr O'Malley has been clinical director of the women's service since 1917

Dr Gerald Webb (Fellow), Colorado Springs, addressed the Chicago Tuberculosis Society, January 8, on "Laennec"

Fellows of the American College of Physicians who participated in the Symposium on Gallbladder Disease is conducted by Northwestern University Medical School December 17, before the Chicago Medical Society, were Doctors Andrew C Ivy and Charles A Elliott, both of Chicago

Dr Virgil I Simpson (Fellow) Louisville, recently addressed the Southwestern Kentucky Medical Association at Middlesboro on "Modern Methods of Handling the Diabetic Patient"

Dr Simpson also addressed the Lee-County Medical Society (Taylor Green and Adair Counties, Ky) December 4 on "Menstrual Disorders and Pelvic Inflammation"

## College News Notes

ident of the above-named Society The Society will meet regularly on the first Tuesday of each month, from October to April

Dr L F C Wendt (Fellow), Detroit, addressed the members of the Woman's Auxiliary of the Wayne County (Detroit) Medical Society, December 9, on "Essential Value of Food in Diet and Dieting"

Dr Grafton Tyler Brown (Fellow), Washington, D C, read a paper on "Periodic Hay-Fever," by invitation, before the Eastern Section of the American Laryngological, Rhinological and Otolological Society's meeting in Atlantic City, January 5. The discussion was opened by Dr Maximilian A Ramirez (Fellow), New York, N Y, and Dr George Piness (Associate), Los Angeles, Calif

The public schools of the cities of East Chicago and Gary, Indiana, have inaugurated Child Guidance Clinics for their problem children, or children with emotional disorders. Problem school citizens will likely become problem social citizens later. The clinics do not undertake the study of the feeble minded or epileptics. Other organic conditions, however, are studied. Child Guidance has raised the good prognosis rate of problem children from 10% to 50%.

Dr H S Hulbert (Fellow), Chicago, goes to Indiana one day a week to conduct these clinics. Educators, pediatricians, sociologists and psychiatrists are invited to attend these clinics by making arrangements.

Announcement has been received that the Charles Godwin Jennings Hospital, successor to the Detroit Diagnostic Hospital, has been completed at a cost of \$800,000, and was opened on November 28. The new hospital is organized as a non-profit corporation governed by a Board of Trustees. It has forty-two private rooms and twelve double rooms.

Dr Frank Smithies (Master) Chicago delivered a public address December 9, at Western Union. What the Public Should Expect from the Hospital and Medical Profession. On December 8, 9 and 10 Dr Smithies presented clinics on medical and

surgical aspects of duodenal ulcer and biliary tract disease at the DeEtte Harrison Detwiler Memorial Hospital at Wauseon. The staff of the Detwiler Memorial Hospital is composed of the entire membership of the Fulton County Medical Society.

Dr George W McCoy (Fellow), National Institute of Health, Washington, D C, is Secretary of the United States Committee of the Second International Congress of Comparative Pathology, which will meet in Paris, France, October 14-18, 1931.

Dr Miles J Breuer (Fellow), Lincoln, Nebr, has recently been appointed head of the Department of Pathology of the Bryan Memorial Hospital.

Dr D P Scott (Fellow), Lynchburg, Va, addressed the South Piedmont Medical Society at Danville (Va), November 25, on "Medical Aspects of Diseases of the Ductless Glands."

At the annual meeting of the Richmond (Va) Academy of Medicine, Dr J Morrison Hutcheson (Fellow) was elected President. Dr Charles M Caravati (Fellow) was elected a Vice President, and Dr Stewart R Roberts (Fellow), Atlanta, delivered a paper on "Thyroid Heart."

Dr Warren T Vaughan (Fellow), Richmond, took part in a symposium on Allergy at the meeting of the Postgraduate Medical Society of Southern Virginia, January 13.

Dr Mason Romaine (Fellow) Petersburg, Va, was elected President of the Petersburg (Va) Medical Faculty at its recent meeting in December.

Dr Paul F Whitaker (Fellow), Kinston, N C, was elected a Vice President of the Seaboard Medical Association of Virginia and North Carolina at Elizabeth City, N C, December 2-4, 1930.

Dr Stewart R Roberts (Fellow), Professor of Clinical Medicine at Emory University School of Medicine, Atlanta, addressed the senior medical students of the Medical College of Virginia at Richmond, December 10 on Exophthalmic Goiter.

## OBITUARY

## Oscar Dowling

Dr Oscar Dowling, one of the original members of the American College of Physicians and a former president of the Louisiana State Board of Health, was dramatically killed aboard one of the railroad ferries crossing the Mississippi River at New Orleans on the night of January 2, 1931. From the information that the coroner was able to elicit and from deductive reasoning, there being no witnesses of the event Dr Dowling evidently while attempting to board the train on the ferry slipped and was carried under the wheels. It was some hours before his body was discovered.

The death of Dr Dowling removes from the state of Louisiana and the South one of the most active medical men in this section. He was for many years head of the State Board of Health and did a tremendous service in improving sanitation in Louisiana and New Orleans. Dr Dowling was a fearless prosecutor of what he considered wrong. At times his methods were spectacular, but he went ahead without fear or favor in doing what he thought was right for the community as a whole. He fought persistently and steadily for the elevation of preventive medicine and for public health ideals. Contemporaries who followed Dr Dowling through his years of service with the State Board of Health testify as to how he improved health conditions in Louisiana and to the difference that exists today as contrasted with the time when he presided over it.

For some years Dr Dowling was Professor of Hygiene at Tulane University. He served as a member of the Board of Trustees of the American Medical Association for twelve years and was chairman of the Section on Preventive and Industrial Medicine and Public Health in 1924-25. Dr Dowling had a wide circle of friends throughout the country. These men knew him as a charming, congenial southern gentleman, one who invariably had definite ideas concerning very broad fields which he never hesitated to advance if he had the opportunity. (Furnished by J H Musser, M D, New Orleans, La.)

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Dr Edward Franklin Leonard (Fellow) Chicago, Ill., died, October 31, 1930, of heart disease, aged, 58 years.

Dr Leonard was born at Cincinnati, Ohio. His records show that he matriculated in the College of Physicians and Surgeons of Chicago, the College of Medicine of the University of Illinois, October 3, 1892, upon credentials showing that he had obtained the degree of Doctor of Medicine from the Harvey Medical College of Chicago, Illinois, in June, 1902. Upon these credentials, he was advanced to the fourth year class and received his degree of Doctor of Medicine from the University of Illinois on May 26, 1903. He was Instructor in Neurology on the Faculty of the College of Medicine of the University of Illinois from 1913 to 1916 when he was advanced to the rank of Assistant Professor,



and remained on the Faculty in this Department until 1921

Dr Leonard was the author of many articles published in various medical journals. He was a member of the Chicago Medical Society, the Illinois State Medical Society, the American Medical Association, the Illinois State Hospital Medical Society, the Chicago Neurological Society, and had been a Fellow of the American College of Physicians since January 30, 1920

#### Doctor George Morris Golden

The sudden and untimely death from heart disease of Dr G Morris Golden on January 12, 1931, marks a distinct loss not only to the Hahnemann Medical College and Hospital of Philadelphia where he was Professor and head of the Department of Medicine but also to the entire medical profession of which he was a distinguished member

Dr Golden was comparatively a young man at the height of a successful career. His personality, executive ability and broad scientific knowledge gained for him a reputation among his colleagues and profound admiration by all with whom he came into contact. He was especially loved and respected by his students and patients for whom he gave his all. He was a tireless worker and student himself and invariably believed that the best time to do a thing was now. He disliked procrastination and for success's sake, self was a secondary consideration. He was a conscientious observer and thoroughly recorded scientific data and, although he did not write books, he spoke frequently on medical subjects and contributed extensively and com-

mendably to medical literature through medical journals

Dr Golden was born in Philadelphia, Pa, March 14, 1876, educated in the Public Schools and Central Manual Training School and at the University of Pennsylvania. He received his degree in Medicine from the Hahnemann Medical College of Philadelphia in 1899

Since graduation, he has been associated with the Medical Department of the Hahnemann Medical College and Hospital. For many years he was Clinical Professor of Medicine and for the past five years has been Professor and Head of the Department of Medicine. He was also Chief of the Medical Staff of the St Luke's and Children's Homeopathic Hospital of Philadelphia and Consulting Physician to several institutions. He was a past President of the Eastern Homeopathic Medical Association and the Homeopathic Medical Society of the State of Pennsylvania

Dr Golden was elected to Fellowship in the American College of Physicians in 1929 and was an active member of the Philadelphia County Homeopathic Medical Society, the Homeopathic Medical Society of the State of Pennsylvania, the American Institute of Homeopathy and the Germantown Medical Society. He was also a member of the Unanimous Club of New York, the Fortnightly Club and the Phi Alpha Gamma Fraternity. He is survived by his widow, Mrs Lorana Mattix Vanneman Golden, two daughters and a twin brother, E Lewis Golden of Reading, Pennsylvania

(Furnished by Carl V Vischer, M.D., F.A.C.P., Philadelphia, Pennsylvania)

# Non-Development of Eosinophilia in Pernicious Anemia Patients Treated With Desiccated Stomach\*

By S. M. GOLDBAUMER, M. D., *Ann Arbor, Michigan*

THE possibility of producing remissions in pernicious anemia under controlled conditions by the use of liver, liver extracts or stomach has opened the way for the careful study of the changes in the blood as the condition improves. The present paper deals with the changes in the eosinophilic content of the blood. Minot and Murphy<sup>1</sup> noted that after a liver diet the polymorphonuclear eosinophile leucocytes occasionally increased to 20% or more, the rise persisting for many weeks. Whitby<sup>2</sup> reported an eosinophilia in four patients treated with raw or cooked liver. He felt that there was a relationship between the

clear neutrophils and eosinophiles appear in greater numbers. One case showed a rise to 25% after one month of liver diet. Watkins and Beiglund<sup>3</sup> reported a relatively constant percentage of eosinophiles up to the 18th day and then a marked increase ranging from 2 to 48% after this. They attributed this to a systemic reaction following an overdose of liver. Meulengracht and Holm<sup>4</sup> reviewed the literature of the subject and reported their own experience. They divided their patients into 3 groups, those receiving raw liver, cooked liver, and liver extract.

They found that a typical ex-

American Medical Association at Detroit, reported a very high eosinophilia in a patient treated with dried stomach. In Levine and Ladd's<sup>7</sup> series of 143 patients with pernicious anemia, 54 showed 5% or more eosinophiles at some time during the course of their disease, some reaching 25 per cent. These patients were not treated with liver or stomach tissue.

In order to note whether an eosinophilia was in any way related to the active principle which stimulates blood maturation in pernicious anemia or to some other constituent of liver, and to see whether it was also present in stomach tissue, the blood of 30 patients with typical pernicious anemia, who were being treated with dried stomach, was studied daily. The stools were examined with care to eliminate the possibility of infestation with intestinal parasites.

### DATA

It was found that no gross eosinophilia above 5% developed in any patient who did not have any eosinophilia at the start. Of 6 patients with eosinophilia at the beginning of the treatment 2 had asthma or hay fever, 1 came from a family in which near relatives had asthma, and 2 had skin lesions. In one patient with a high eosinophile percentage (8.5—13%) before treatment no cause could be found. The presence of eosinophilia in patients of this type is a noteworthy fact as the polymorphonuclear neutrophils and basophilic leucocytes are frequently relatively, and usually absolutely decreased in number during the leucopenia of the relapse in pernicious anemia. The pernicious anemia

process does not inhibit the development of eosinophiles.

The average eosinophile percentage during the first 30 days of treatment with desiccated stomach, including all cases (both those with a high eosinophile percentage and the others) did not exceed 3.2%. This mixed group did not produce an average eosinophilia above 4.5% during the period of 8 to 16 weeks after the beginning of treatment (37 observations). Excluding the patients with an initial eosinophilia (i. e. above 5%) the average maximum for the first 30 days of treatment was 2.2%, and in 32 observations on this group during the next six months the highest average was 2.7%.

Of all the patients not showing an initial eosinophilia, two developed 8% eosinophiles, one on the 12th day of therapy, and not thereafter, and the other on the 11th day only. One showed 25% eosinophiles on one occasion at the end of the second month of treatment. The data concerning the number of eosinophile cells were compared to the red blood cell counts, the reticulocyte percentage and number, the hemoglobin percentage, and the total white blood cell count, and no simple correlation was evident.

### SUMMARY AND CONCLUSION

1. No constant eosinophilia develops after treatment of pernicious anemia patients with desiccated stomach tissue.

2. In patients with allergic phenomena (asthma, hay fever, skin lesions), fundamental changes associated with pernicious anemia do not prevent the development of the character-

istic eosinophilia commonly seen in these conditions

3 Eosinophilia may be present in pernicious anemia in the absence of an evident cause, and this sign is not a differential feature in the diagnosis of uncomplicated pernicious anemia and infestation with intestinal parasites

4 There is no correlation between the changes in percentage, or absolute number, of eosinophile cells

and the red blood cell count, hemoglobin percentage, or numerical changes in the reticulocytes

5 The eosinophile stimulating substance of raw liver is not the active hematopoietic principle

6 The eosinophile count cannot be used as a standard or index of the potency of the active blood maturing principle in desiccated stomach or liver extract

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# The Inhibitory Action of Infection and Fever on the Hematopoietic Response in a Case of Pernicious Anemia\*

By KENNETH C SMITHBURN, M D, AND L G ZERFAS, M D, *Indianapolis*

IN THE study of more than 150 cases of primary and secondary anemia, it has been frequently observed that fevers and intoxications of various origins have apparently retarded, interrupted, or prevented the hematopoietic response during active treatment. Minot<sup>1</sup> has pointed out that the hematopoietic response in cases of pernicious anemia treated with liver extract may be slight or delayed in the presence of complications. Whipple and his associates<sup>2</sup> have observed that infections and intoxications may retard the increase in hemoglobin production in experimental anemias.

The following patient, who came under our observation, demonstrates in a striking manner the effect of infection and fever on the response of the blood forming organs.

## REPORT OF CASE

*History.* L. I., a white female, aged 53 years, a housewife, was admitted to the Indianapolis City Hospital on April 1, 1930, complaining of weakness, numbness and tingling in the ex-

trémities, sore mouth and tongue, icterus, constipation, dyspnea and palpitation on exertion. She first became ill in 1928, with nausea, vomiting, and epigastric pain. She lost strength rapidly and noticed that her skin was yellow. Her appetite became very poor and the sense of taste was markedly impaired. This condition persisted with temporary periods of remission until September 1929, when she first noticed sensations of numbness and tingling in her fingers and toes, the weakness became more extreme, and was accompanied by dyspnea and palpitation on slight exertion. About this time, also, nocturia, with pain and burning near the termination of urination, began. The patient's memory for details became very poor, she was markedly depressed and discouraged on admission to the hospital. She stated that her diet had consisted of fruits and vegetables and that she did not care for meats. She had lost about fifty pounds in weight in two years.

The past history was entirely negative. She was married at twenty-one, but had no pregnancies. The climacteric occurred in 1927. The family history was irrelevant.

\*Jolly Laboratories for Clinical Research, Indianapolis City Hospital and Department of Medicine, Indiana University.

### *Physical Examination*

The skin and conjunctivae were of a lemon yellow color and were quite pale. The lingual papillae were atrophic, there were numerous channels over the tongue. All the natural teeth were absent. There was a soft systolic murmur over the mitral area. The blood pressure was 120 systolic and 62 diastolic. The spleen was palpable 3 cm below the costal margin. The reflexes were normal. Otherwise the physical findings were essentially negative.

### *Laboratory Examination*

The erythrocyte count was 1.76 million, the leukocyte count 4,600 per cubic millimeter of blood, the hemoglobin 31.2% (Newcomer), and the reticulocyte (young red blood cell) count 2.1% (36,960 per cubic millimeter). The stained blood smears revealed the presence of many macrocytes typical of those observed in pernicious anemia during relapse. The blood bilirubin was 0.66 milligram per 100 cubic centimeters and the diazo test showed a delayed positive reaction. The blood Wassermann was negative. The gastric analysis showed an absence of free hydrochloric acid and blood. The urinalysis showed specific gravity 1.017, reaction alkaline, albumin a trace, 20 pus cells per high power field, centrifuged a few trace cells.

A diagnosis of pernicious anemia was made.

this dose was maintained throughout the period of treatment. On April 14, the reticulocyte count had increased to 15% (250,500) and there was corresponding clinical improvement. On the following day the patient complained of frequency, urgency, burning on urination, and pain over the urinary bladder. The temperature, which had been within normal limits, rose to 102° and the urine was loaded with pus and bladder epithelial cells. The reticulocyte count decreased to 10.9% (191,750). On April 17 she had a severe chill lasting about one hour, followed by a sharp rise in temperature to 106°, accompanied by nausea and vomiting. There was severe pain and marked tenderness in the region of the left kidney, urinalysis showed many pus cells and bladder epithelial cells and a considerable amount of albumin. The total non-protein nitrogen of the blood and the phenolsulphonephthalein test were normal. Leukocyte count was 4,000. Supportive treatment was given, and elimination was aided by the usual means. The response of the blood was completely inhibited during this attack of pyelitis and cystitis.

Following this acute illness the patient improved steadily. The temperature reached normal on April 23 but rose temporarily to 103.6° this time attended by much less severe constitutional symptoms, and returned to normal on April 26. The urinary find-

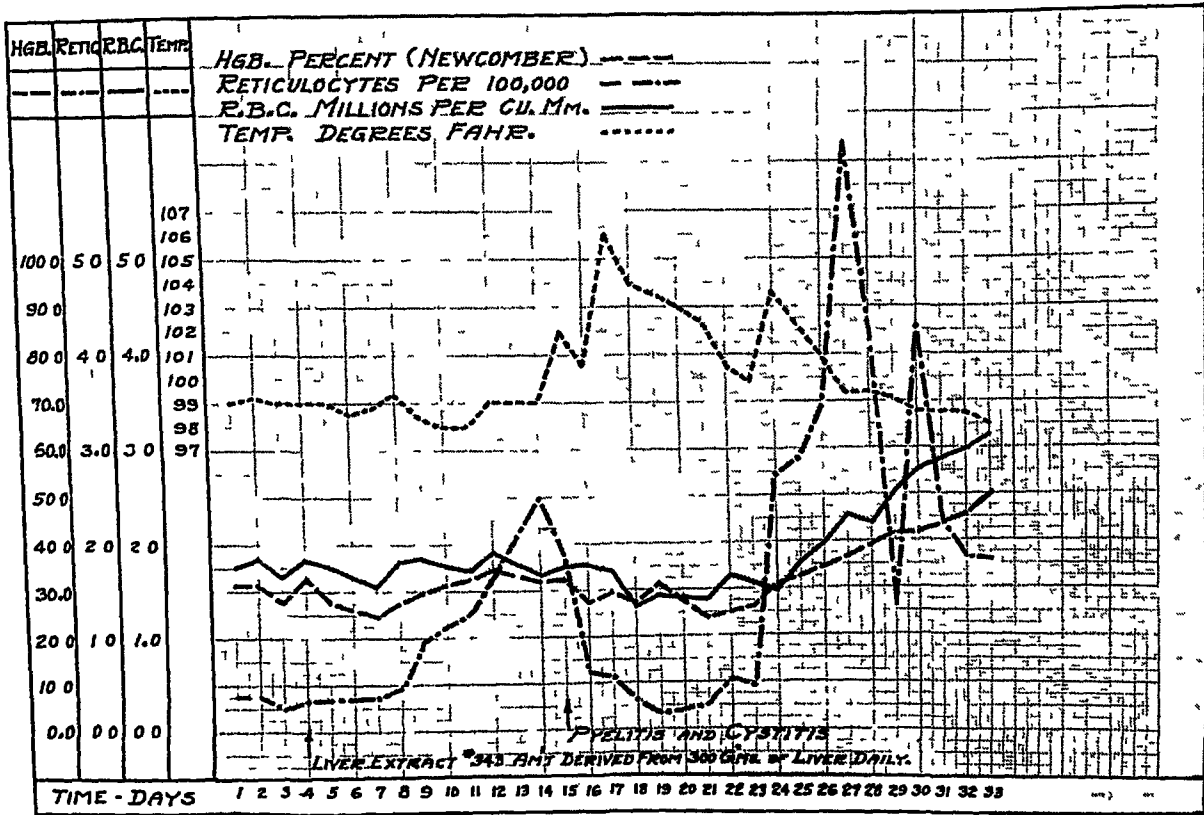


Chart I shows the levels of temperature, hemoglobin, erythrocytes, and reticulocytes before and during treatment, the inhibition of the hematopoietic response during the attack of pyelitis and cystitis, and recovery with a secondary reticulocyte response. The temperatures given are the highest recorded for the given day.

creased rapidly and there was marked improvement in the general condition of the patient. She was released from the hospital on May 6, 1930. At this time the red blood cell count was 3.12 million, the reticulocyte count was 5.8% (180,920) and the hemoglobin was 50%. Her appetite was good, the bowels regular, the color much improved, and she stated that she felt very well.

Zerfas and others have shown that, in cases of pernicious anemia treated with liver extracts in adequate daily amounts, the average erythrocyte count at the end of one month's treatment is approximately 3.5 million, regardless of what low level the count may

have reached before treatment was started. It is interesting to note that, in the case here reported, the red blood cell count at the end of one month's treatment was but 0.38 million below what would normally be expected, despite the fact that the response was suppressed for twelve days of this month.

COMMENT

In this case the control period of eleven days before the occurrence of fever seems to demonstrate clearly the inhibitory effect of fever or infection on the activity of the blood forming organs. Furthermore, the striking response occurring immediately follow-

ing subsidence of the fever and infection indicates clearly the advisability of continuing the daily administration of adequate amounts of liver extract in cases of pernicious anemia complicated by infection and fever

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# The Possible Significance of the Thymus Gland in the Syndrome of Hyperthyroidism\*

By HARRY M. MARGOLIS, M. D., *Fellow in Medicine, The Mayo Foundation, Rochester, Minnesota*

IT IS significant that in reviewing the many reports concerning the relation of the thymus gland to hyperthyroidism one finds relatively few reports of careful histologic study of the affected glands. In most cases thymic hyperplasia is assumed merely on the basis of the increased weight of the thymus gland as compared with the weight of the normal gland. However, it is now well known, particularly as a result of the extensive and careful researches of Hammar<sup>11</sup>, that one cannot draw accurate conclusions of the structure of the thymus gland, by a consideration merely of its weight. Histologic studies aiming to determine the structural characteristics and, to some extent the quantitative relations of the various constituents of the thymic parenchyma and interstitium, are essential to determine the existence of pathologic hyperplasia or involution. Furthermore, such pathologic changes as are found in the various constituents of the thymus gland should be correlated with the salient clinical features in each case if the more obvious relationships between the thymus gland

and the hyperthyroid syndrome are to be crystallized. For these reasons, a thorough investigation of the thymus gland in a series of cases of hyperthyroidism in which complete pathologic and clinical data were available was undertaken. The present report is concerned with the results of this investigation.

## REVIEW OF LITERATURE

Subsequent to the report of Moebius, more than a century ago, Markham described a typical case of exophthalmic goiter in which at necropsy the thymus gland was found remarkably enlarged. Mackenzie, in a review of thirty-six cases of exophthalmic goiter in which necropsy was performed, found the thymus gland considerably enlarged in a fair number of these. He said "The most constant feature next to the enlarged thyroid is the presence in most cases of a persistent or enlarged thymus gland." He observed, however, in some cases that "although the gland was large, it showed the histological changes not of actively enlarged gland, but rather those of degeneration or some degree of fibrosis was present, but in other instances, it appeared like the gland of a child." Gierke claimed that enlarged

\*Work done in the Section of Pathologic Anatomy, The Mayo Clinic. Submitted for publication May 1, 1939.

thymus glands are more common among patients dying soon after thyroidectomy than among the general group of thyrotoxic patients. Matti, reviewing the literature in a large number of cases of hyperthyroidism, also showed the common occurrence of thymic hyperplasia in patients dying after thyroidectomy. Similar reports on the frequent association of thymic hyperplasia and goiter have been made by Warthin, Crotti, Blackford and Freligh, Giordano, Potter and others. Potter regards the reaction of the thymus gland as a part of the lymphoid reaction characteristic of exophthalmic goiter. Klose and Warthin go so far as to assume that thymic hyperplasia is an invariable factor in the syndrome of hyperthyroidism. The absence of thymic hyperplasia in acute cases of long standing does not, according to Klose, preclude such a possibility. He suggests the possibility of secondary involution changes in the thymus gland incidental to the altered nutritional state of such patients and postulates the existence of aberrant thymus tissue that may be undergoing hyperplastic change.

Von Haberer has stressed the significance of partial thymectomy along with partial thyroidectomy in the treatment of hyperthyroidism. Although he often observed recurrence

for thymic hyperplasia, had occasion to perform seventy-five thymectomies. Melchior, on the other hand, could not find any relation between the enlarged thymus gland frequently seen in hyperthyroidism and the course of the disease, or the postoperative results. He pointed out that recurrences following combined operations on the thymus and thyroid glands are just as frequent as when thyroidectomy alone is performed.

Among reports of histologic studies on the thymus gland in hyperthyroidism are those of Bayer who described marked broadening of the cortex and medulla with almost complete disappearance of the boundary between the cortex and medulla. Hassall's corpuscles were extraordinarily numerous and showed varying degrees of degeneration. Kocher indicated that histologically the thymus gland in cases of exophthalmic goiter is identical with that seen in juvenile hyperplasia of the thymus gland. Hammar's<sup>13</sup> studies showed that there was usually a marked increase in the cortical portion of the parenchyma, and a definite increase in the number of Hassall's corpuscles. Occasionally he stated, the hyperplasia is confined to the medulla, and the quantitative relations between cortex and medulla are altered in favor of the medulla.

clinical data left no doubt of the diagnosis and in most cases the clinical diagnosis was confirmed by the pathologic condition of the thyroid gland either at the time of operation or at necropsy. In certain cases in which undoubted clinical evidence of hyperthyroidism was present, stained sections revealed little evidence of hyperplasia in the thyroid gland. This was more often true of hyperfunctioning adenomatous goiter than of exophthalmic goiter. The clinical criteria on which were based the differentiation of exophthalmic goiter and hyperfunctioning adenomatous goiter were those established largely through the work of Mayo and Plummer. It may be noted that in nearly all cases in which exophthalmic goiter was diagnosed clinically some degree of diffuse parenchymatous hyperplasia and hypertrophy of the epithelium of the thyroid gland was found pathologically, whereas in cases diagnosed clinically adenomatous goiter with hyperthyroidism extra adenomatous hyperplasia of the thyroid epithelium was rarely encountered. In several cases of frank exophthalmic goiter adenomas were also present in the thyroid gland, but they were thought not to influence appreciably the production of the hyperthyroidism.

In all but eight of the fifty-five cases of exophthalmic goiter, some degree of hyperplasia of the thymic parenchyma was noted (table 1). In these eight cases there was either marked involution, or the entire thymic parenchyma had become replaced by fibro-areolar connective tissue which was entirely devoid of thymic cells or contained only scattered small thymic

cells. It is notable that among the forty-seven cases in which there was thymic hyperplasia the gross weight of the thymus gland had increased in only twenty-eight. In the other nineteen cases the size of the thymus gland was not remarkable and the existing hyperplasia could not be detected without histologic study. On the other hand, of the eight cases in which striking involution was evidenced histologically, there was a definite increase in the weight of the thymus gland in four cases. Indeed, in one of these cases the gross weight of the thymus gland was 148 gm, the largest weight recorded for any of the thymus glands in the entire series. However, histologic studies of numerous sections from this gland proved it to be composed almost entirely of fatty-areolar tissue. It becomes obvious from this fact that the diagnosis of thymic hyperplasia must be reserved always until both gross and histologic studies of the thymus gland have been made.

The degree of thymic hyperplasia when it does occur in exophthalmic goiter is extremely variable. Similarly, marked variation in the degree of hyperplasia of the various components of the thymic parenchyma is also found in various hyperplastic glands.

Perhaps the most striking phenomenon in the study of hyperplastic thymus glands in the cases of exophthalmic goiter, is the occurrence in a certain number of them of thymus glands which structurally resemble those seen in infants. In the present series, twelve of the forty-seven hyperplastic glands presented this appearance. The lobular arrangement of the thymus gland in such cases is re-

TABLE I  
SUMMARY OF DATA IN CASES OF LYOPHTHIRMIC COLIC

[illegible]

TABLE I—Continued

Case	Sex, Years	Duration of Symptoms, Months	Basal Metabolic Rate	Weight, Pounds	Loss of Weight, Pounds	Significant Associated Conditions	Weight of Gland, Gm	Histologic Appearance	Comment
20	10F	3	+31	110	2	Bronchopneumonia	36	Fibrosis and large islets of hyperplastic cortical thymic tissue	On verge of crisis
21	18F	24	+81	133	19	None			
22	50M	3	+57	164	41	Bronchopneumonia			
23	22F	36	+80	150		Bronchopneumonia	98	Marked degree of medullary hyperplasia, considerable increase in number and size of Hassall's corpuscles, slight fibrosis	Diabetes, mild hyperthyroidism
24	37M	11	+24			Diabetes mellitus			
25	72M	24	+20	88	47	Bronchopneumonia			Recurrent hyperthyroidism, partial thyroidectomy three times previously
26	13F	132	+79			Abscess of lung			
27	66M	8	+64	124	31	Bronchopneumonia	21		
28	17F	33	+88	110	26	Septicemia	37	Marked degree of fibrosis	Recurrent hyperthyroidism, partial thyroidectomy two months previously
29	50F	14				None			Recurrent hyperthyroidism, lobectomy previously
30	13F	120	+38	109	31	Pneumonia			Recurrent hyperthyroidism, partial thyroidectomies three times previously
31	26F	3				None			In crisis
32	43F	12	+147	133	27	Metrorrhagia	8	Small islets of hyperplastic medulla with marked increase in number and size of Hassall's corpuscles, marked degree of fibrosis	Recurrent hyperthyroidism, lobectomy previously
33	32F	15		95	40	Bronchopneumonia	21		
34	74M	18	+37	141	56	Bronchopneumonia			
35	43F	4	+71	86	34				
36	36F	18	+35	108	37	Encysted empyema			
37	32M	24	+86	143	22	Passive congestion			Recurrent hyperthyroidism, lobectomy previously
38	40M	60	+102	185		Pulmonary infarction			Severe hyperthyroidism
39	58M	3	+61	132	63	Bronchopneumonia	24		



markably regular. These lobules are divided by rather thin fibrous trabeculae and there is little, if any, evidence of preexisting involution. The cortex is rather sharply demarcated from the medulla which in most cases seems proportionately diminished in amount. The cortical tissue is considerably increased in amount, producing a rounded, bulging outer contour to each lobule. The cortex is densely packed with deeply staining, small thymic cells. In the medulla, the most striking feature is a marked increase both in the number and in the size of Hassall's corpuscles. These corpuscles vary considerably in size, some being composed of only two or three swollen, hyalinized cells, while others appear relatively huge and are composed of concentric layers of cells. Nearly every corpuscle shows an advanced degree of

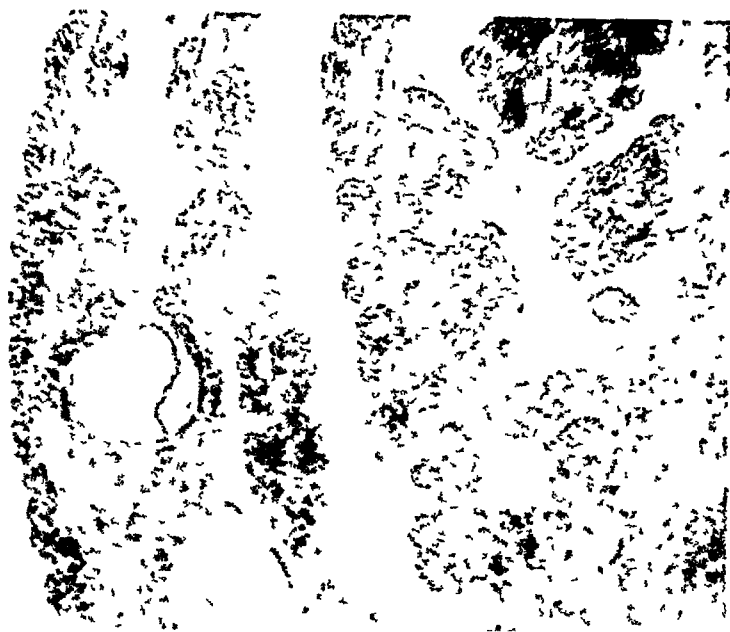
degeneration, the component cells being usually of hyaline character. Calcification in these corpuscles is rarely seen, and only rarely does one encounter what might appear to be recently formed corpuscles, so uniform is the process of degeneration in them. The entire picture is strikingly similar to an infantile type of thymus gland except for the marked increase in the number and in the size of Hassall's corpuscles (fig. 1).

Among the other thymus glands of this series in which hyperplasia was found, there was, besides the hyperplasia, evidence of a variable degree of preexisting involution with a corresponding degree of replacement of fibrous tissue. In eight cases, the thymus gland showed large islets of hyperplastic cortical tissue, with a relatively slight degree of medullary hyperplasia



(fig 2) These irregularly shaped islets of thymic parenchyma were separated by considerable amounts of fatty-areolar connective tissue which we must assume represent the result of the preexisting involution. In three of these eight glands the degree of parenchymatous hyperplasia was marked, whereas in the other five glands, the fibrous tissue was more abundant and the degree of parenchymatous hyperplasia somewhat less pronounced. In all cases, there was a very striking increase in the number and in the size of Hassall's corpuscles which was identical with that seen in the infantile type of thymus gland. In two additional cases, the islets of hyperplastic tissue were represented almost entirely by cortical substance, the medulla being relatively small in amount and Hassall's corpuscles normal in size and in number.

In nineteen cases, hyperplasia was confined to the medulla, there being only a narrow rim of cortical substance bordering the islets of parenchyma (figs 3 and 4). In seven of these cases the degree of medullary hyperplasia was considerable and the amount of connective tissue relatively smaller in amount than in the remaining twelve cases in which the fibrosis was more marked and the islets of hyperplastic medulla correspondingly smaller in size. It is in this group of cases that the characteristic changes in Hassall's corpuscles appear in a most striking manner. In general, the changes in the corpuscles are essentially those already described as occurring in the infantile type of thymus gland. However, here the size of the corpuscles frequently assumes tremendous proportions, some being so large that they occupy the





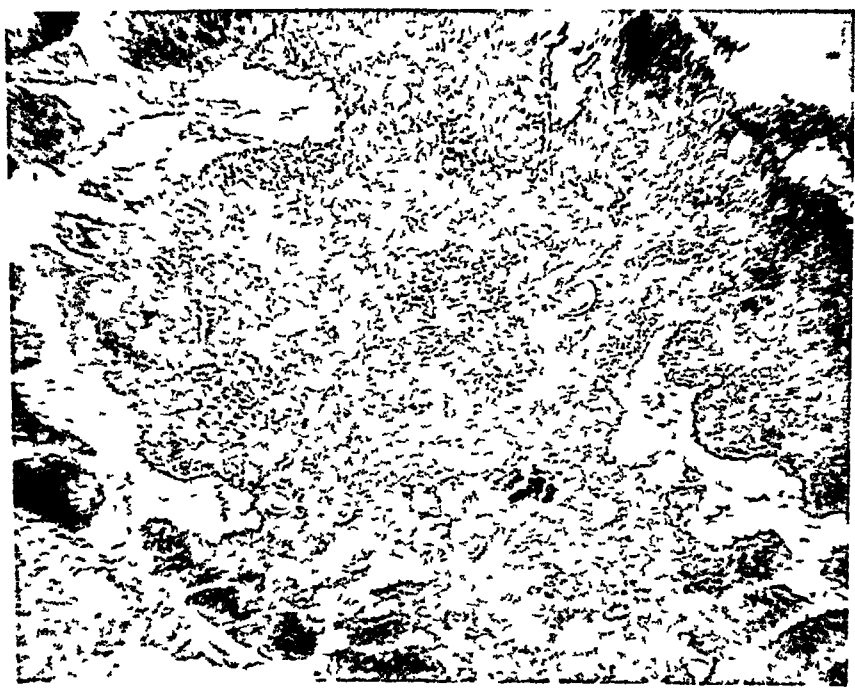
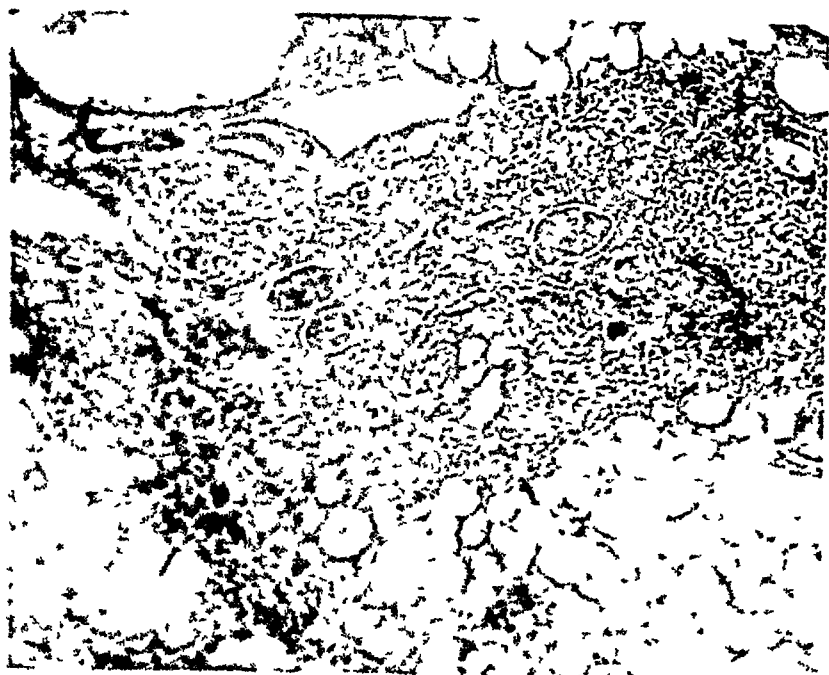


FIG. 3 Section of thymus gland showing marked medullary hyperplasia, increase in the number and size of Hassall's corpuscles and fibrosis in a girl aged twenty-two years who died from exophthalmic goiter ( $\times 12$ )

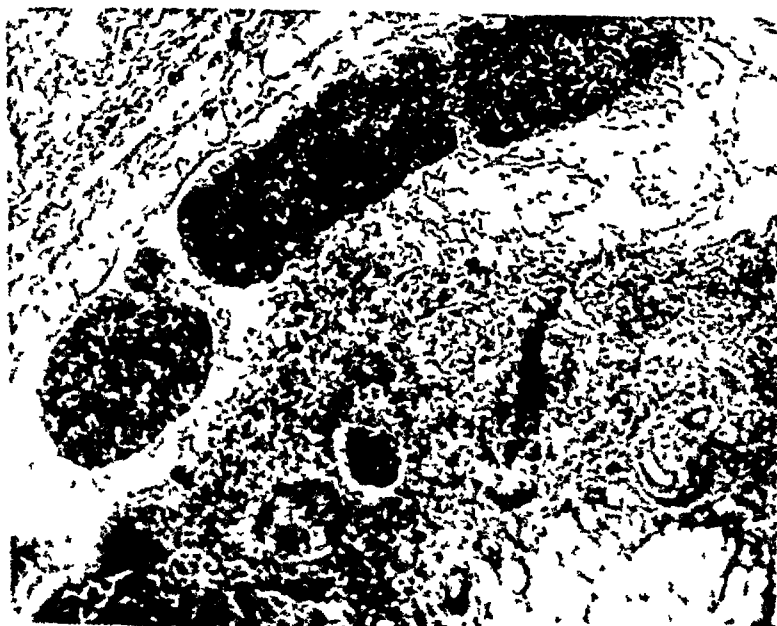


greater portion of a high-power microscopic field. Frequently several corpuscles of varying sizes are found to be fused, forming conglomerate masses of hyalinized tissue in which the cellular outlines are not discernible. The degenerative process in these corpuscles must be proceeding at a rapid pace, for it is extremely unusual to find Hassall's corpuscles in which an advanced degree of hyaline degeneration has not occurred. Surprisingly, calcification of these hyalinized corpuscles is not often encountered. The reticular epithelium is quite abundant and often it is closely aggregated about well formed Hassall's corpuscles, forming concentric layers of well defined epithelium. In some cases the reticular epithelium shows widespread degeneration; the cytoplasm of the cells appearing swollen and having a glazed

appearance suggesting early hyaline change. In one case such reticular epithelial cells appeared as if lying free in the epithelial network, the nucleus large and vesicular and the cytoplasm swollen and almost hyaline in appearance.

In six cases of this group, the islets of parenchyma showed an equal degree of hyperplasia in the cortex and medulla, with an increase in the number and in the size of Hassall's corpuscles, and varying degrees of fibrosis (fig 5). Occasionally, some evidence of hemorrhage was noted within the thymus gland of patients who died shortly after thyroidectomy.

In summarizing the pathologic observations of the thymus gland in the fifty-five cases of exophthalmic goiter it may be noted that parenchymatous hyperplasia was found in forty-seven

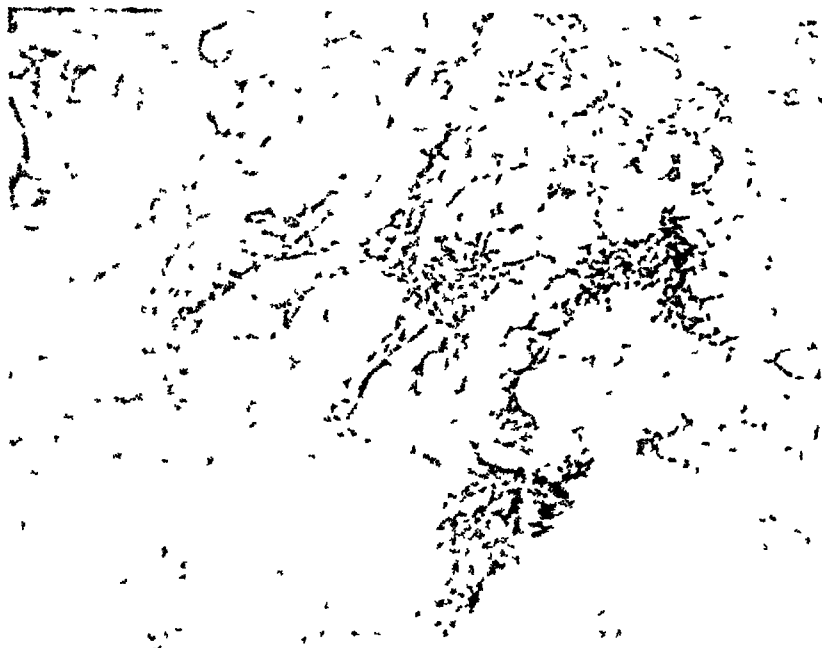


(85 per cent) In twelve cases (22 per cent), the thymic structure resembled that seen in the thymus gland of the infant, except for an increase in the number and size of Hassall's corpuscles In thirty-five cases, (63 per cent), hyperplasia had occurred in glands which had previously undergone varying degrees of involution and fibrosis In the group of forty-seven cases the hyperplasia was either confined exclusively to the cortex or the cortical hyperplasia predominated in twenty-two cases (47 per cent), medullary hyperplasia was the predominant finding in nineteen cases (40 per cent), and the hyperplasia was equally distributed between the cortex and the medulla in the remaining six cases (13 per cent) In all except two cases in which parenchymatous hyperplasia occurred, a marked increase in the number and in the size of Hassall's

corpuscles was a prominent histologic feature Eight cases (15 per cent) showed either far advanced involution without evidence of hyperplasia or the entire thymic mass was composed of fatty areolar connective tissue (fig 6)

Of the thirty cases of adenomatous goiter with hyperthyroidism sixteen cases, (53 per cent) showed some degree of hyperplasia, whereas fourteen cases showed advanced involution without any evidence of hyperplasia (table 2)

None of the cases exhibited the infantile type of thymus gland, so often seen in hyperplastic thymus glands of patients with exophthalmic goiter. In every instance in which hyperplasia of the thymus gland was found in cases of hyperfunctioning adenomatous goiter there was present also evidence of preexisting involution and fibrosis Furthermore, in all except two of the



thymus glands of this group showing hyperplasia, the medulla alone had undergone hyperplastic change. The cortical tissue was extremely scanty in amount if, indeed, it was definitely present. These islands of medullary tissue varied in size and were separated by considerable amounts of fatty areolar connective tissue (figs 7 and 8). In only three cases was the medullary tissue present in considerable amounts, in the other cases the hyperplastic medulla constituted only small islets of parenchyma embedded in a rather large amount of fatty areolar stroma. In addition to these cases showing medullary hyperplasia, the thymus gland in one case showed small islets of hyperplasia affecting both the cortex and medulla and in one case islets of cortical tissue

alone were present, the medulla being almost entirely absent. In all of these glands in which medullary hyperplasia was present (fifteen of the sixteen glands in which hyperplasia occurred) Hassall's corpuscles were increased in number and in size. The hyperplasia of these corpuscles, the changes in their size and the tendency to degeneration was essentially identical with that seen in the thymus gland in cases of exophthalmic goiter. One exception to this was the definitely exaggerated tendency to the occurrence of calcification of Hassall's corpuscles in these glands which contrasted with the condition in the thymus glands in cases of exophthalmic goiter.

Fourteen of the thirty cases of adenomatous goiter with hyperthyroidism (47 per cent) showed an ad-



TABLE 2  
EXPERIMENTAL GOITER WITH HYPERTHYROIDISM

Associated Conditions	Weight of Gland, Gm	Histologic Appearance	Comment
	6	Moderate degree of medullary hyperplasia, considerable increase in number and size of Hassall's corpuscles, marked degree of fibrosis	
	2	Marked fibrosis, small islets of medullary tissue containing increased number of Hassall's corpuscles many of which showed hyaline degeneration and calcification	
	10	Marked fibrosis, small islets of cortical tissue Moderate degree of fibrosis, islets of medullary and cortical hyperplasia with increased number and size of Hassall's corpuscles	Ligation of superior thyroid arteries previously



vanced degree of involution without any evidence of hyperplasia (fig 9) In five of these glands small remnants of the thymic parenchyma could be seen, whereas in the others only occasional, scattered small thymic cells could be found It should be noted again that among these cases in which involution was practically complete, three cases revealed glands the gross weight of which was increased Such glands would ordinarily be assumed to constitute evidence of thymic hyperplasia if their true nature were not looked for in histologic sections

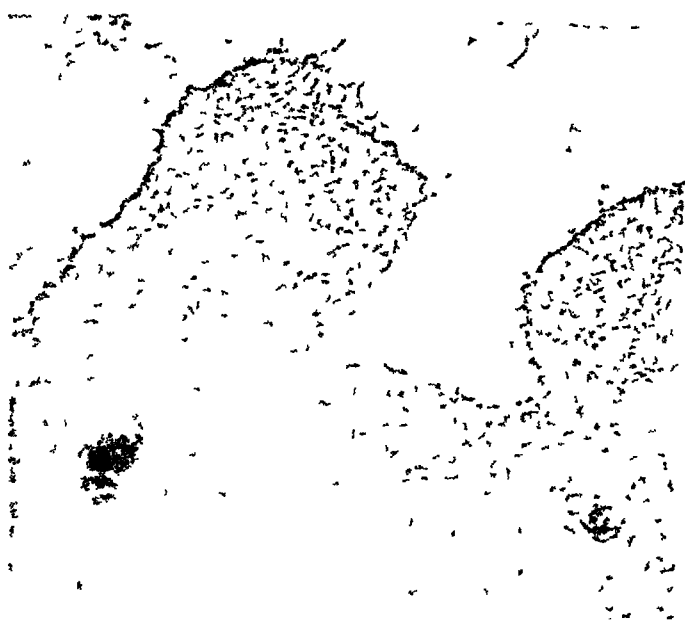
#### COMMENT

The variability of the pathologic changes in the thymus glands in the group of cases of exophthalmic goiter

and, more particularly, the contrast in the reactions between the glands in exophthalmic goiter and in hyperfunctioning adenomatous goiter, deserve consideration For the present, one may seek an explanation for this variable reaction of the thymus gland first of all in those factors which have been proved to have definite influence on the reactions of the thymus gland

In view of the fact that the most significant physiologic influence affecting changes in the thymus gland is that associated with advancing age, it seemed necessary to analyze the influence of this factor in this group of cases

In the cases of exophthalmic goiter the age of the patients varied from six-



teen to seventy-four years, the average age was forty-four years. In the group of adenomatous goiter with hyperthyroidism the ages varied from forty-seven to seventy-four years, the average age was sixty years. It would seem that the more advanced age of the patients with adenomatous goiter might, to a certain extent, account for the uniformly higher incidence of preexisting involution in the thymus gland of such patients. One might suspect that for the same reason hyperplasia of the thymus gland when it does occur in these cases is also uniformly less pronounced. That this is not, however, the entire explanation for the discrepancy becomes evident from a more detailed analysis of the age factor in the vari-

ous types of hyperplasia within the group of cases of exophthalmic goiter. In the cases of exophthalmic goiter in which the hyperplasia was extremely marked, the group which showed practically no evidence of involution, the ages varied from sixteen to fifty-two years, the average being thirty-five years. This in itself points to an anomalous influence at least in certain patients with exophthalmic goiter, an influence which tends to inhibit for many years, and to a remarkable degree, the involution process of the thymus gland which normally begins at puberty. It may be noted that the average age of the patients with exophthalmic goiter, in whom parenchymatous hyperplasia occurred in glands





which also showed preexisting involution, was forty-six years. Moreover, in the cases of exophthalmic goiter in which involution of the thymus gland was the outstanding feature, the age of the patients was still higher, varying from forty-three to sixty-two years, the average age in this group was fifty-one years. Thus, it seems that in general, the age at which hyperthyroidism becomes manifest does, to a certain extent, determine the degree of preexisting involution in the thymus gland, and, similarly, the degree of parenchymatous hyperplasia. Nevertheless, there is a striking exception to this in the group of cases in which the thymus gland does not show involution even at middle age.

That disease conditions, particularly infectious processes, which may be associated with hyperthyroidism, particularly in patients who die after the operation, do not have any significant bearing on the condition of the thymus gland is apparent. It may be seen in tables 1 and 2 that in general patients with marked hyperplasia of the thymus gland had complications of an infectious nature as frequently as did those in which the thymus gland showed only slight hyperplasia or complete involution.

without hyperplasia the average duration of the symptoms of hyperthyroidism was only slightly higher, namely thirty-three months. In the series of cases of exophthalmic goiter more striking data are available. Thus, the average duration of symptoms in the cases of extreme parenchymatous hyperplasia without involution was only eight and three-tenths months, in those cases in which a variable degree of hyperplasia was associated with evidence of preexisting involution, the average duration of symptoms was twenty-nine months, whereas in cases in which hyperplasia was entirely absent, the average duration of symptoms was considerably higher, almost nine years.

Klose suggested that the explanation for the absence of thymic hyperplasia may lie in the altered nutritional state of patients who had had hyperthyroidism for a long time. Evidence obtained in my study does not support this hypothesis, although it might be suspected that the loss of weight might parallel the duration of the disease process. In fact, analysis of the data in my series of cases does not reveal any appreciable difference in loss of weight among the patients who had had hyperthyroidism for years as compared with those in whom the symptoms of thyrotoxicosis were of relatively short duration. Neither was there any correlation between the amount of weight lost and the variable pathologic picture in the thymus gland. Thus, the average loss of weight in cases of exophthalmic goiter and marked thymic hyperplasia was 25 pounds, whereas in those in which the hyperplasia was moderate or absent, and, in those with involution, the aver-

age loss was 30 pounds and in those cases in which hyperplasia did not occur, the average loss recorded was even lower, 27 pounds. The same relationship holds true in the cases of adenomatous goiter with hyperthyroidism. It is obvious, then, that in my series of cases the loss of weight associated with the hyperthyroidism cannot be invoked as a cause for the variable degree of hyperplasia or involution in the thymus gland. This suggests the possibility that the duration of the hyperthyroid state causes, in some other manner, the variable pathologic picture in the thymus gland or that the variable duration of the symptoms in hyperthyroidism is, indeed, the consequence of a variable severity of the disease, dependent in turn, on a variable physiologic status of the patient—a status in which the condition of the thymus gland is but one evident index. In other words, the degree of thymic hyperplasia in hyperthyroidism, particularly in exophthalmic goiter, may be but the expression of a variable constitutional state of the patient, indicating a variable degree of susceptibility or predisposition to the

merit of being most consistent with the facts in my series of cases, as I shall illustrate presently.

If thymic hyperplasia does, indeed, represent an index of a constitutional state in an individual, indicating susceptibility to the development of hyperthyroidism, then the degree of thymic hyperplasia in such cases might be expected to follow step-by-step with the severity of the disease when it becomes established. My study indicates that this is actually the case, if the severity of the disease is estimated by the incidence of thyrotoxic crisis and by the incidence of recurrence of hyperthyroidism following thyroidectomy. In the twelve cases of exophthalmic goiter in the series in which extreme hyperplasia occurred, five patients were in a state of crisis when admitted to the clinic, one patient suffered a severe hyperthyroid reaction postoperatively, and still another patient came for the treatment of recurrent hyperthyroidism which developed some time after thyroidectomy for exophthalmic goiter. In the group of thirty-five cases of exophthalmic goiter in which parenchymatous hyperplasia in the thymus

seven patients with exophthalmic goiter in whom hyperplasia of the thymus gland was found, thirteen patients had been in a state of crisis, two patients had had hyperthyroid reactions postoperatively, and nine patients had had recurrent hyperthyroidism. In contrast with this is the group of eight cases of exophthalmic goiter in which involution of the thymus gland was found. Although the duration of the hyperthyroidism in this group was much longer than in the previous group, on an average nearly nine years, crisis occurred in only one case and in none was there a history of recurrent hyperthyroidism following thyroidectomy. Similarly, in the entire group of cases of adenomatous goiter with hyperthyroidism, in which the degree of thymic hyperplasia was uniformly less pronounced than in cases of exophthalmic goiter, a hyperthyroid reaction occurred postoperatively in one case and hyperthyroidism recurred in only one case. In both of these cases the thymus gland showed involution which may be accounted for by the advanced age of these patients, which was twenty-four and fifty-nine years respectively.

functioning adenomatous goiter, generally with only slight degrees of hyperplasia, a more benign form of the disease develops for which medical advice is not sought for years, and yet the patients remain relatively immune to the severe manifestations of thyrotoxic crisis and are less subject to recurrence of the hyperthyroidism following thyroidectomy.

My data do not permit a definite answer to the question of whether hyperplasia of the thymus gland precedes or follows the onset of the thyrotoxic state. Certain facts are, however, suggestive. In most cases in which the hyperplasia occurs, there is definite evidence of preexisting involution, and the irregular distribution of the islets of hyperplastic parenchyma suggests that they had developed subsequent to involution. On the other hand, in the group of cases in which I have described the thymus gland as conforming, in certain respects, structurally, to the infantile type of gland, the implications are different. The lobular arrangement in such glands is so uniformly regular, the fibrous septums so thin, and the absence of much fibrous tissue so conspicuous that it seems inconceivable that this infantile structure had been reconstructed so perfectly following previous involution. The appearance of such glands makes one suspect that they had maintained their normal structure throughout the average span of thirty-five years, at which age these patients were observed at The Mayo Clinic. If this is true, the thymus gland in these cases had maintained an autonomy of existence for many years subsequent to the onset of puberty, at which time

physiologic involution usually begins. The impression one gains from the study of the thymus gland in these cases of hyperthyroidism is that hyperplasia probably exists in many cases for years before the onset of the symptoms of hyperthyroidism. Some evidence which I have presented does, however, indicate that hyperplasia of the thymus gland probably occurs also following the development of the disease, as seems evident by the cases in which involution had occurred previously. The degree of hyperplasia which is maintained or the degree to which involution of the thymus gland will proceed in such cases, may depend on the variable intensity of some inherent factors in the potentially hyperthyroid state. The factors or influences which might inhibit the involution process or produce hyperplasia of the thymus gland in such cases are entirely unknown, and must, for the present, be ascribed to a certain constitution of the individual, a term the meaning of which is still somewhat vague, but one which may, in the future, be much more clearly defined. This theory is not a new one. The influence of "human constitution" in disease has been suspected for centuries. Attempts at quantitative evaluation of this factor in disease of man is a product of modern medicine. The

cent years. Certain observers have stressed the occurrence of lymphoid hyperplasia in patients with exophthalmic goiter. Boit, among others, reported cases of hyperthyroidism in which lymphoid hyperplasia was a prominent feature of the pathologic changes. According to Warthin, Chvostek was among the first to consider the existence of a definite constitution underlying the condition of exophthalmic goiter. From a study of pathologic material in which he frequently noted lymphoid hyperplasia within the thyroid gland and in other lymphoid structures, Warthin, too, concluded that "the constitutional defect of the thymic-lymphatic (Graves') constitution underlies every case of exophthalmic goiter and toxic adenoma". That lymphoid hyperplasia is common in cases of hyperthyroidism is well known. What its relationship is to the hyperplasia in the thymus gland cannot at present be told. If it is assumed that the thymus gland is an epithelial structure and most of the evidence seems to point to this, then it would seem logical to view lymphatic hyperplasia and thymic hyperplasia as dual manifestations of some underlying influence rather than as an anatomically integral factor by which the hyperthyroid constitution might be symbolized.

syndrome of hyperthyroidism The interpretation of Bircher's experimental data on inducing toxic symptoms in the dog by the implantation of hyperplastic thymic tissue, must be reserved until more is known regarding the physiology of the thymus gland in normal individuals Knowledge of the physiologic functions attributed to the thymus gland have been gleaned from experimental studies on lower animals, and most of these have yielded contradictory evidence In a brief critical review on the physiology of the thymus gland, Hoskins said "Whatever be the real function of the thymus, certain it is that its production of an internal secretion has not been proved The evidence in favor of such a theory is but circumstantial at best and very meager" In view of the largely equivocal evidence which still shrouds the results of physiologic experiments on the thymus gland, I am, for the present, entirely in accord with this view.

#### Summary and Conclusions

The thymus gland frequently presents parenchymatous hyperplasia in hyperthyroidism In general, the degree of hyperplasia is much more pronounced in cases of exophthalmic goiter

than in cases of adenomatous goiter with hyperthyroidism

Cortical hyperplasia is most common with exophthalmic goiter although medullary hyperplasia, alone or combined cortical and medullary hyperplasia, also occurs In hyperfunctioning adenomatous goiter, medullary hyperplasia is most characteristic

An increase in the number and in the size of Hassall's corpuscles is nearly always seen in glands that show parenchymatous hyperplasia

True hyperplasia of the thymus gland may not be inferred from an increase in its gross weight alone Histologic studies are essential to confirm such a diagnosis

The occurrence of hyperplasia of the thymus gland may represent the expression of a constitution indicative of an inherent predisposition to the development of hyperthyroidism The degree of such hyperplasia may be roughly proportional to the degree of such susceptibility to the development of the disease

It is impossible at present to evaluate the direct physiologic relationship that may exist between the thymus and thyroid glands in the syndrome of hyperthyroidism

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# The Effect of Irradiated Ergosterol on the Thrombocytes and the Coagulation of the Blood\*

By R. A. PHILLIPS, M. D., D. F. ROBERTSON, M. D., W. C. CORSON, M. D.  
AND G. F. IRWIN, M. D., *St. Louis, Mo*

IT has of course been known since the work of Zizzozzio and Wooldridge that the thrombocytes are a definite factor in aiding coagulation and with their increase it has been shown by Duke<sup>1</sup> that the coagulation time of the blood is diminished. Gunn<sup>2</sup> with the ultra-violet light produced an increase of thrombocytes in rabbits. "The increase varied from 40%-100% of the original normal but always amounted to at least twice that of the normal variation in the animal." It occurred to us in considering this latter work that this action might be due to the vitamin D affected on the body surface by the irradiation. Since irradiated ergosterol offered another source of vitamin D it seemed advisable to study its effect on the thrombocytes of mammals when ingested by them in varied amounts.

Both rabbits and white rats were tried as experimental animals but we found that the control counts in the latter were more constant. Cramer, Drew and Mottram<sup>3</sup> have reported what they consider to be the normal

thrombocyte and erythrocyte counts for white rats and our figures agree with theirs. We also tried both the direct and indirect method of counting thrombocytes and soon found the latter to be much the more satisfactory and reliable. The actual method (most of the essentials are taken from Sooy and Laurens<sup>4</sup>) used finally, is as follows:

(1) The rat's tail is thoroughly cleansed with soap and water and then dried.

(2) A thin coating of vaseline, to prevent any remaining particles from entering the solution, is applied to the tail.

(3) 8 cc of the diluting fluid, described by Rees and Ecker<sup>5</sup>, 3.8% sodium citrate, 0.2% brilliant cresyl blue, are placed in a clean 10 cc "Wassermann" test tube.

(4) With vaseline coated scissors from 0.5 to 1.0 cm is snipped from the tip of the rat's tail and the tail is then quickly immersed in the diluting fluid and a solution of sufficient concentration obtained. (After familiarizing one's self with the method a concentration of about the normal human erythrocyte count dilution is readily ob-

\*From the Department of Surgery, Washington University School of Medicine and Barnes Hospital, St. Louis, Mo.)

tained This number allows a ready discernment of the thrombocytes )

(5) The tube is then covered with a vaseline-coated thumb of one of the investigators and inverted and re-inverted for 2 minutes (The 2 cc air bubble insures equal mixing) Care was taken to omit shaking since it was found that the results that followed were erratic The counting chamber of a hemocytometer was then loaded with the suspension and a minimum of 400 erythrocytes and the thrombocytes in the same area counted Each count was done in duplicate, thus checking one against the other and the average of the two used in the results

(6) A careful erythrocyte count was also obtained from the tail at regular intervals

(7) A silk ligature is tied around the tail about a quarter of a centimetre from the cut end to control any bleeding from the artery

(8) The animals who were fed the irradiated ergosterol received the dosage in drops approximately 3 drops to the minimum

Tables I and II show 2 series of 5 animals each with the initial and final erythrocyte counts and the thrombocyte counts on successive days Table II has a group of rats who received a series of control counts 3 weeks before they received the irradiated ergosterol, as a further check on the constancy of the normal control results

whom experimental counts were first run were noticed to lose considerable blood if the stumps of the tails were not ligated

The response to the irradiated ergosterol was just as had been anticipated The control animals, as is seen, held a very normal variation throughout while all of the animals receiving the irradiated ergosterol increased their thrombocytes 47%-353%, depending on the dosage administered It would seem that the rise is, at least in part, due to an actual increased production since the maximum effect is not reached for several days and the duration of the thrombocytosis is for an even greater period of time, even though the drug is discontinued To date we have not been able to determine this satisfactorily but we are working on phases of the problem and hope to be able to report more of this at a later date

Fig 1 is an illustrative graph of the block type showing the minimum variation of the thrombocytes in the white rats before and after receiving irradiated ergosterol and the maximum variation of the control animals (Included are the thrombocyte variations of the series studied especially for coagulation and charted in tables III, IV and V) The results here are quite conclusive but perhaps not as striking as they might have been had the second group been given a further 1000



TABLE I

1		2		3		4		5	
Initial erythrocytes	Thrombocytes	Dose	Thrombocytes	Dose	Thrombocytes	Dose	Thrombocytes	Dose	Thrombocytes
Final	8,530,000		9,575,000		8,650,000		8,265,000		8,710,000
Date	7,030,000		9,430,000		9,010,000		8,390,000		8,980,000
3/21/29	0	0	1,116,000	0	910,000	0	818,000	0	904,000
3/22/29	0	0	1,243,000	0		0	918,000	0	889,000
3/23/29	0	0	957,000	0	895,000	0	860,000	0	750,000
3/24/29	0	0		0	1,011,000	0		0	800,000
3/25/29	0	3		10				10	
3/26/29	0	3		10				10	
3/27/29	0	3	2,054,000	10	1,829,000	0	842,000	10	1,890,000
3/28/29	0	3	1,994,000	10	1,622,000	0	971,000	10	1,300,000
3/29/29	3	3	3,520,000	10	1,482,000	0	926,000	10	1,320,000
3/30/29	3	3	3,240,000	10	1,720,000	0		10	1,870,000
3/31/29	0	3	3,720,000	10	1,508,000	0		10	1,320,000
4/1/29	0	0	4,710,000	3	1,365,000	0		10	1,370,000
4/2/29	0	0	5,630,000	3	1,829,000	0		10	1,675,000
4/3/29	0	0	3,750,000	3	2,205,000	0		10	1,742,000
4/7/29	0	0	2,910,000	3	1,402,000	0		10	1,450,000
4/18/29	0	0	2,714,000		1,254,000		917,000	10	1,146,000

\* Dosage is in drops of Aetrol (viosterol Mead, furnished through the courtesy of Mead, Johnson & Co.)

TABLE II

6		7		8		9		10	
Initial erythrocytes	Thrombocytes	Dose	Thrombocytes	Dose	Thrombocytes	Dose	Thrombocytes	Dose	Thrombocytes
Final	9,995,000		10,110,000		9,170,000		9,790,000		9,750,000
Date	9,921,000		9,900,000		9,300,000		8,960,000		9,370,000
3/19/29	0	0	909,000	0		0		0	
3/20/29	0	0	1,060,000	0	1,070,000	0		0	
3/31/29	0	0	1,070,000	0	1,023,000	0	1,090,000	0	1,100,000
4/2/29	0	0	1,230,000	0	1,208,000	0	1,250,000	0	1,360,000
4/3/29	0	0		0		0	1,026,000	0	1,320,000
4/20/29	1	2	1,060,000	0	1,150,000	0	910,000	6	1,050,000
4/21/29	1	2	1,720,000	0	1,470,000	0	1,260,000	6	1,640,000
4/22/29	1	0	1,250,000	0	1,170,000	0	1,270,000	9	4,160,000
4/23/29	0	0				0	1,130,000	0	3,300,000

were found to be effective but they were apparently much less so in the time tried. It is particularly interesting to note that number 3 who was receiving 10 drops had a good increase but that there was an even greater increase when the dosage was decreased to 3 drops. Number 5 also had a less marked increase than rats 1, 2 and 3 indicating that too large a dose seems to have some sort of an inhibiting influence after the initial response.

The series, of course, is small, but our point, that the irradiated ergosterol did increase the thrombocytes, seemed to be proven, and with that our attention was obviously turned towards coagulation.

Previous experimental work has been done which would indicate that

irradiated ergosterol should have a depreciatory effect on the coagulation time. Brougher<sup>6</sup> found that cod-liver oil effected a decreased coagulation time in dogs. Sooy and Moise<sup>7</sup> have successfully treated several patients with purpura by exposing them to the quartz light. Selye<sup>8</sup> has reported that when vitaminol is given internally to white rats, there is an instant hastening of the coagulation time. There are no figures given in this short article.

The investigation of methods of coagulation was confined to the micro-methods since we were working with such small animals. The two methods finally selected were the Moise and Sooy<sup>9</sup> capillary tube method and the Boggs<sup>10</sup> method. The former was finally discarded as the control re-

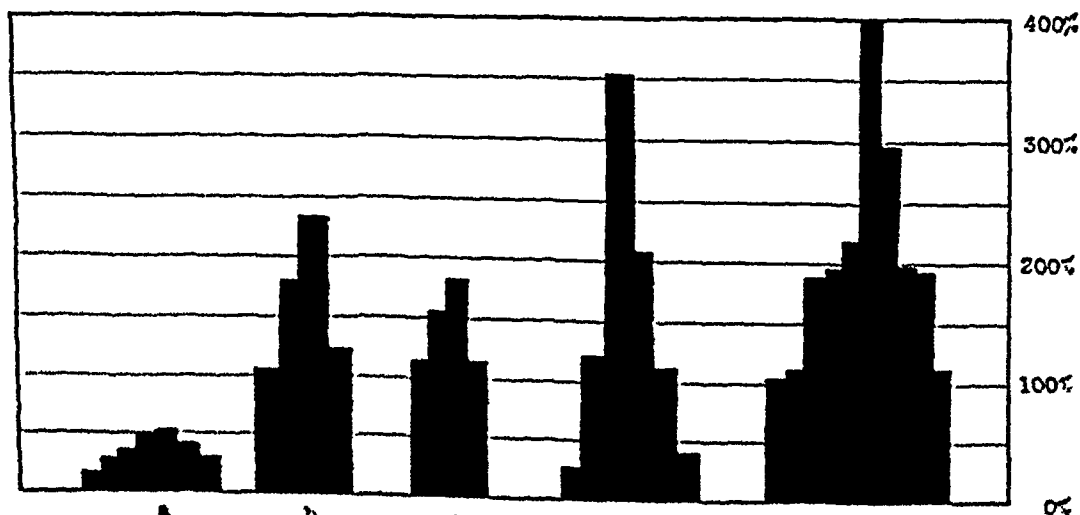


TABLE III

Initial erythrocytes		21		22		23		24	
Date	Dose	Thrombocytes	C.T.	Dose	Thrombocytes	Dose	Thrombocytes	Dose	Thrombocytes
10/23/29	0	482,000	2'15"	0	600,000	0	582,000	0	689,000
10/24/29	0	518,000	3'00"	0	573,000	0	568,000	0	598,000
10/25/29	0	113,000	2'45"	3	570,000	3	453,000	3	520,000
10/26/29	3	518,000	2'15"	3	677,000	3	545,000	3	880,000
10/27/29	3	711,000	1'30"	3	806,000	3	605,000	3	1,107,000
10/28/29	3	690,000	1'15"	3	1,147,000	3	855,000	3	1,024,000
10/29/29	3	1,335,000	1'15"	3	1,630,000	3	879,000	3	1,082,000
10/30/29	3	1,402,000	1'15"	3	1,850,000	3	1,080,000	3	1,059,000
10/31/29	3	1,710,000	1'00"	3	1,640,000	3	1,150,000	3	1,175,000
11/ 1/29	3	1,732,000	1'00"	3	1,235,000	3	1,240,000	3	1,521,000
11/ 2/29	3	2,463,000	0'45"	3	1,405,000	3	1,285,000	3	1,126,000
11/ 3/29		1,715,000	1'00"	0'45"	1,975,000		1,165,000		1,186,000

C.T. -- Coagulation time in minutes and seconds

TABLE III

Initial erythrocytes		25		26	
Date	Dose	Thrombocytes	C.T.	Dose	Thrombocytes
10/23/29	0	621,000	2'15"	0	623,000
10/24/29	0	689,000	2'15"	0	530,000
10/25/29	0	532,000	2'30"	0	510,000
10/26/29	0	587,000	2'15"	0	617,000
10/27/29	0	600,000	2'15"	0	680,000
10/28/29	0	698,000	2'00"	0	673,000
10/29/29	0	720,000	2'30"	0	652,000
10/30/29	0	565,000	2'15"	0	702,000
10/31/29	0	623,000	2'00"	0	663,000
11/ 1/29	0	642,000	2'15"	0	678,000
11/ 2/29	0	665,000	2'00"	0	590,000
11/ 3/29		602,000	2'15"		601,000

8,550,000 C.T.  
8,220,000  
8,730,000 C.T.  
8,500,000

TABLE IV

Initial thrombocytes	Dose	Thrombocytes	C.T.	Dose	Thrombocytes	C.T.	Thrombocytes	C.T.
11,400	0	711,000	2'00"	0	779,500	2'00"	750,000	2'00"
11,140	0	761,000	2'00"	0	625,000	2'15"	664,000	1'45"
11,120	3	702,000	2'00"	3	765,000	2'15"	700,000	2'00"
11,160	0	1,059,000	1'15"	3	1,200,000	1'45"	1,397,000	1'15"
11,140	0	1,115,000	1'30"	3	1,208,000	1'15"	1,110,000	1'15"
11,140	0	1,117,000	1'30"	3	1,127,000	1'00"	1,510,000	1'00"
11,140	0	2,000,000	1'15"	3	2,215,000	0'45"	1,580,000	0'45"
11,140	0	2,150,000	1'00"	3	1,665,000	1'00"	3,132,000	0'15"
11,140	0	1,370,000	1'15"	3	1,327,000	1'00"	2,128,000	0'15"
11,140	0	1,415,000	1'30"	3	1,216,000	1'15"	1,690,000	0'45"
11,140	0	1,011,000	1'45"	3	1,025,000	1'15"	1,010,000	1'30"
11,140	0	1,170,000	1'30"	3	1,136,000	1'45"	1,275,000	1'30"

TABLE IV

Initial thrombocytes	Dose	Thrombocytes	C.T.	Dose	Thrombocytes	C.T.	Thrombocytes	C.T.
11,140	0	547,000	2'15"	0	712,500	2'00"	625,000	2'30"
11,140	0	570,000	2'00"	0	827,000	1'45"	715,000	2'30"
11,140	3	1,067,000	1'30"	3	1,282,000	1'30"	603,000	2'30"
11,140	3	1,007,000	1'15"	3	802,000	2'30"	475,000	2'15"
11,140	3	1,600,000	1'15"	3	916,000	2'00"	619,000	2'00"
11,140	3	1,301,000	1'15"	3	1,118,000	1'15"	698,000	2'30"
11,140	3	2,800,000	0'45"	3	1,322,000	1'00"	505,000	2'15"
11,140	3	1,610,000	1'15"	3	2,250,000	0'45"	515,000	2'15"
11,140	3	1,710,000	1'30"	3	1,585,000	1'00"	607,000	2'15"
11,140	3	1,501,000	1'30"	3	1,350,000	1'15"	637,000	2'00"
11,140	3	1,020,000	1'00"	3	912,000	1'45"	655,000	2'15"
11,140	3	1,300,000	1'00"	3	1,186,000	1'30"	514,000	2'15"

TABLE V

Initial erythrocytes		H		42		43		44	
Final	Date	Dose	Thrombocytes	C.T.	Thrombocytes	Dose	Thrombocytes	C.T.	Thrombocytes
12/ 2/29	12/ 2/29	0	745,000	1'15"	626,000	0	620,000	2'30"	679,000
12/ 3/29	12/ 3/29	0	712,000	2'15"	560,000	0	501,000	2'30"	587,000
12/ 4/29	12/ 4/29	3	840,000	1'15"	444,000	3	500,000	2'00"	602,000
12/ 5/29	12/ 5/29	3	917,000	1'15"	1,322,000	3	743,000	1'45"	965,000
12/ 6/29	12/ 6/29	0	1,000,000	1'30"	1,115,000	0	1,250,000	1'15"	979,000
12/ 7/29	12/ 7/29	0	1,825,000	0'15"	1,230,000	0	920,000	2'00"	1,108,000
12/ 8/29	12/ 8/29	0	1,215,000	1'00"	1,075,000	0	1,058,000	1'30"	1,236,000
12/ 9/29	12/ 9/29	0	1,500,000	0'15"	1,219,000	0	1,310,000	0'45"	1,425,000
12/10/29	12/10/29	0	2,345,000	0'30"	1,230,000	0	1,126,000	1'15"	1,734,000
12/11/29	12/11/29	0	1,000,000	0'45"	830,000	0	1,286,000	1'00"	1,521,000
12/12/29	12/12/29	0	1,075,000	1'30"	1,012,000		1,315,000	0'45"	1,202,000
12/13/29	12/13/29		1,123,000	1'30"	989,000		1,139,000	1'00"	

TABLE V

Initial erythrocytes		45		46		47		48	
Final	Date	Dose	Thrombocytes	C.T.	Thrombocytes	Dose	Thrombocytes	C.T.	Thrombocytes
12/ 2/29	12/ 2/29	0	668,000	1'45"	610,000	0	678,000	2'30"	564,000
12/ 3/29	12/ 3/29	0	499,500	1'45"	655,000	0	702,000	2'15"	582,000
12/ 4/29	12/ 4/29	0	700,000	1'45"	620,000	3	664,000	2'30"	679,000
12/ 5/29	12/ 5/29	0	561,000	1'45"	889,000	0	790,000	2'00"	1,138,000
12/ 6/29	12/ 6/29	0	561,500	2'15"	1,176,000	0	976,000	1'45"	1,210,000
12/ 7/29	12/ 7/29	0	558,000	1'45"	1,234,000	0	964,000	1'45"	1,026,000
12/ 8/29	12/ 8/29	0	650,500	2'15"	1,102,000	0	1,304,000	1'15"	1,076,000
12/ 9/29	12/ 9/29	0	735,000	2'00"	1,327,000	0	1,573,000	1'00"	1,320,000
12/10/29	12/10/29	0	494,000	1'45"	1,269,000	0	1,310,000	1'00"	1,420,000
12/11/29	12/11/29	0	593,000	1'45"	1,062,000	0	1,239,000	1'30"	1,197,000
12/12/29	12/12/29	0	672,000	2'00"	979,000	0	1,252,000	1'45"	978,000
12/13/29	12/13/29				1,080,000		1,103,000	1'30"	946,000

sults with the Boggs' method were found, in our hands, to be more consistent. The Boggs' coagulometer was hence used in all of the results tabulated below.

(1) The first 4 steps of the procedure outlined above are followed out.

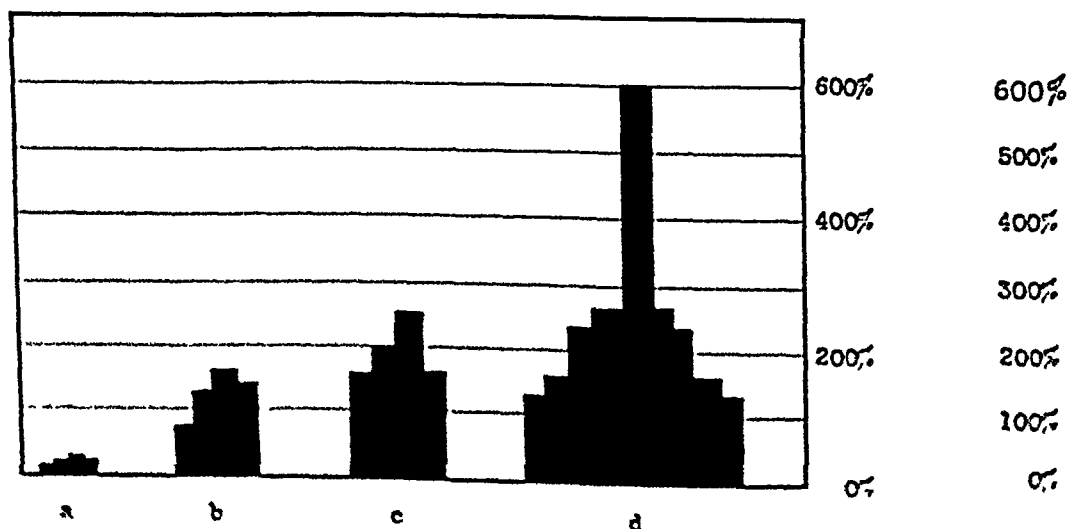
(2) The tail is then wiped off with a clean cloth and the tip is touched to the upper base of the inverted truncated cone of the Boggs' coagulometer. A drop of blood is obtained which just covers the surface, i. e., the attempt is made to obtain approximately the same size of drop each time. The inverted cone is then placed in its receptacle and observed under the 16 mm objective of the microscope.

(3) A current of air is then directed upon the edge of the drop every 15 seconds and the movement of the cells

in the drop is observed with the microscope. Coagulation is assumed when the cells move en masse and spring back to their original position.

(4) Boggs' original method was modified to this extent, the stream of air was directed through a large wash-bottle immersed in a water bath which was kept between  $38^{\circ}$  and  $40^{\circ}$  C. The temperature of the incoming air was thus maintained at a practically constant temperature. The room temperature varied between  $26^{\circ}$ - $27.5^{\circ}$  C.

Three series of animals are reported. One series of 6 white rats, table III, and 2 series of 8 white rats each, tables IV and V. Erythrocyte counts were done daily and the thrombocytes determined by the indirect method described before. To evaluate the results more readily a block graph, Fig. II, is given showing the effect on the con-



trol animals and on the animals receiving irradiated ergosterol It is then seen that a dose of 3 drops on 2 consecutive days is nearly as effective as daily doses in decreasing the coagulation time but not as effective as the

daily dose in increasing the thrombocytes

Fig III and Fig. IV are multiple graph charts of control animal No 45 and animal No 42, who received 3 drops of viosterol on the third and

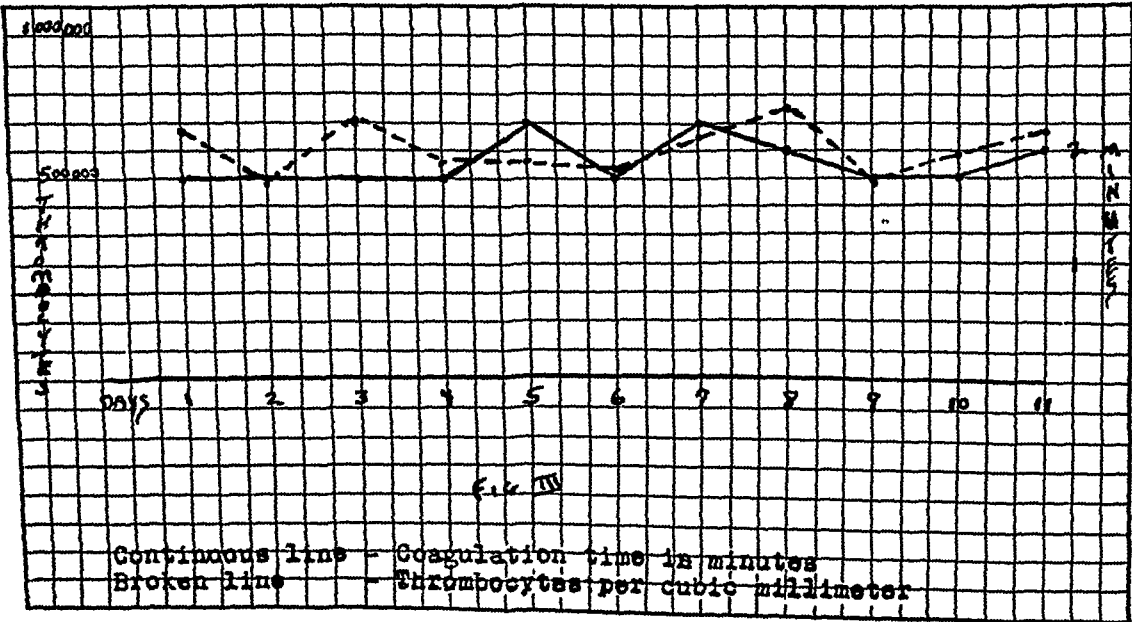


FIG 3

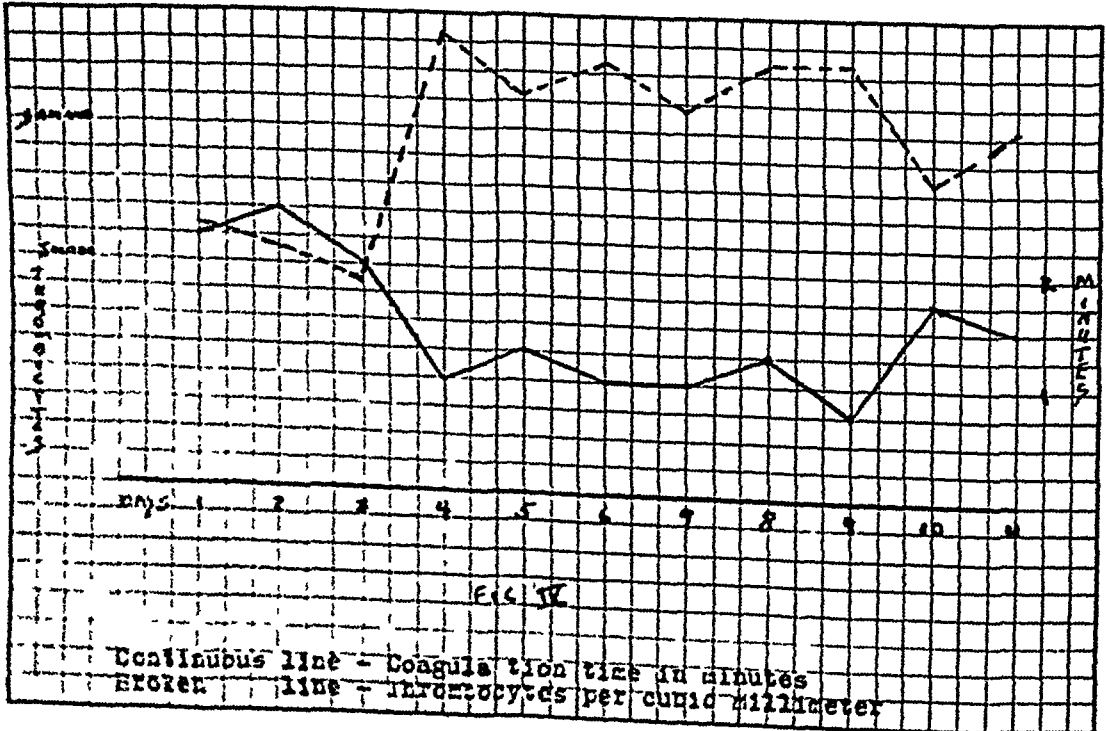


FIG 4

fourth days only. These charts show the close association of the thrombocyte and coagulation time variations. To date sections of the liver, spleen, lung and heart of rats who have been sacrificed after receiving the irradiated ergosterol for some time have failed to show any thrombi. Consequently it would seem that a proportionate single dose could be used very effectively on surgical patients a few days before operation. Further studies on larger animals will have to be carried out to determine the exact effect on the bleeding time and the true coagulation time.

#### CONCLUSION

The tables and graphs are self-explanatory and but one conclusion is

drawn, namely, that irradiated ergosterol is responsible for the increase in the thrombocytes and the decrease in the coagulation time in this series of experiments. Of course there is the possibility that non-irradiated ergosterol or other sterols will produce a like effect. This problem is now being studied and will be reported in the near future.

Further studies on the clinical dosage and its effect on the thrombocytes and coagulation time in healthy and pathological humans are now being made by Dr. L. D. Thompson and his co-workers in the Department of Medicine of Washington University, and will be reported soon.

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# Failure of Irradiated Ergosterol to Relieve Parathyroid Tetany\*†

THOMAS FINDLEY, JR., M. D., *Ann Arbor, Michigan*

**T**O DATE very few reports of attempts to treat parathyroid tetany with irradiated ergosterol are available. Stern<sup>1</sup> tells of giving symptomatic relief to a case of fifteen years duration by administering 3-4 mg of vigantol daily, and Brougher<sup>2</sup> reports four cases successfully treated with viosterol in daily doses of from four to forty drops. It, therefore, seems worthwhile to recount our experience with one case, not only because we failed to obtain results with these doses of viosterol, but because there seem to be certain theoretical reasons why irradiated ergosterol alone should not be relied upon in the treatment of parathyroid tetany.\*

*Tetany*.—With Collip's isolation of the parathyroid hormone<sup>3</sup> and Aub's detailed studies of its metabolic properties,<sup>4</sup> the balance of favor seems to have swung away from the adherents of the intoxication theory of parathyroid tetany to the side of those who believe that all the phenomena can be explained on the basis of calcium de-

ficiency. A full discussion of the various theories has been recently published by Dragstedt.<sup>5</sup> The most rational therapeutic measures have therefore been directed toward (a) equipping the patient with an adequate supply of the parathyroid hormone either by the daily injection of the active principle or by actual gland transplant, and (b) raising the serum calcium to its normal level directly by the ingestion of soluble calcium salts or indirectly by the application of vitamin D in its various forms. The difficulties connected with surgical transplantation of parathyroid tissue are obvious while Collip's preparation, invaluable though it is, fails to meet all requirements, because it cannot be taken orally and because, as Aub has pointed out<sup>4</sup>, it is irregular in its effects on different persons and frequently, after prolonged administration, becomes perfectly inert. MacCallum and Voegtlin's original demonstration<sup>6</sup> that animals in parathyroid tetany could be rendered symptom-free by the administration of calcium salts has been so repeatedly verified in the clinic and in the laboratory that it bids fair to remain the basis for any form of therapy.

*Irradiated Ergosterol*.—Although the classical researches of such men as

\*From the Department of Internal Medicine, University of Michigan and the University Hospital, Ann Arbor, Michigan.

†Since this article was written Jacques (Surg. Gyn. and Obst. 1930, 51: 823) has published similar negative results.

McCollum, Windhaus, Hess, Steenbock and others have made it clear that in irradiated ergosterol we have been presented with an agent powerful in its ability to regulate certain phases of mineral metabolism particularly those concerned with calcium and phosphorus, the mechanism by which it produces its effects is quite unknown. Furthermore, since rickets has occupied the attention of most investigators, there are insufficient published data on the metabolic alterations which this preparation exerts on human adults. The literature is full of testimonials as to the efficacy of viosterol in the prevention and cure of rickets<sup>7</sup>, and infantile tetany has likewise yielded in a specific manner<sup>8,9</sup>. Its application to adults has been much less gratifying, however, except in osteomalacia, a disease considered to be a form of severe adult rickets, there are several reports<sup>10,11</sup> which indicate that lack of vitamin D is an important etiological factor. Blunt and Cowan<sup>12</sup> review the few observations that have been made on the effect of antirachitic substances on normal adults and conclude that moderate amounts of vitamin D have no effect upon their calcium and phosphorus metabolism, although Kroc<sup>13</sup> reported that in four healthy adults he obtained an increased urinary excretion of phosphorus by adding 18-30 mg. of vitamin D to a standard diet. Lunt<sup>14</sup> obtained no benefit from cod liver oil in a case of adult tetany apparently dependent upon a functional hypoplasia of the parathyroid glands. I believe the results of its usefulness in the treatment of these conditions as detailed cases of cases, osteitis fibrosa cystica, hyperostosis, pernicious

anemia, etc., are equivocal<sup>15</sup>. Recent studies<sup>16</sup> indicate, however, that cod liver oil is effective in checking the negative mineral balance of pregnant and lactating women. The proven therapeutic value of vitamin D is limited then to rickets, osteomalacia and infantile tetany, three closely allied disorders which, whatever their ultimate etiological factors may turn out to be, are certainly benefited by an increase in mineral retention. The evidence at hand leads one to believe that young organisms and those suffering from avitaminosis D respond to viosterol administration by an increased mineral retention, while normal adults either fail to respond at all to therapeutic doses or, if they do, it is in the direction of an increasingly negative balance.

*Mode of Action*—Many theories have been advanced to explain these apparent contradictions, but only two of them seem to have sufficient data behind them to warrant consideration here. The first of these supposes that irradiated ergosterol increases the absorption of calcium from the intestinal tract, and many efforts have been made to prove that vitamin D by lowering the pH of the intestinal contents changes the insoluble tertiary calcium phosphate  $\text{Ca}_3(\text{PO}_4)_2$ , to the much more soluble acid form,  $\text{CaH}_2(\text{PO}_4)_2$ . It has been realized for a long time that hydrochloric acid will partially heal rickets and many observations<sup>17,18</sup> indicate that frequently but not always the feces of rachitic animals are more alkaline than normal and that vitamin D increases the acidity and lessens the amount of residual calcium of the intestinal contents. Chas-

cal determinations, however, have been even more inconstant<sup>20</sup>. If it should turn out to be that such changes are the essential nature of this vitamin's activity, it is conceivable that the primary alterations occur in the gastric juice, bile, pancreatic secretions, or the succus entericus. Attention must be called to a series of ingenious experiments performed by Bauer and Marble<sup>21</sup>, which they interpret as indicating that viosterol promotes calcium absorption from the intestinal tract. Cats were fed on a low calcium diet, until it was certain that their calcium reserve was much depleted. Amputation of the left foreleg of every cat and fixation of the humeri gave them a permanent record of the state of the animal's mineral reserve at the end of the period of low calcium intake by which they could check further observations. All the cats were then given a diet high in calcium and, in addition half of them received viosterol daily. At intervals thereafter animals were killed and the bone trabeculae of the right humeri compared to those of the previously amputated left legs. In this way, they were able to see the effects on calcium storage produced by high calcium diets with and without viosterol. The authors state that in every instance not only did the high calcium diet increase the calcium reserve, but that viosterol distinctly augmented this reserve. These are certainly important observations, but one feels that they do not take into consideration possible variations in parathyroid activity.

The second theory relates the action of vitamin D to stimulation of the parathyroid glands but, like the first,

is full of apparent inconsistencies. The studies of Aub and his colleagues<sup>4</sup> followed by those of Albright and Ellsworth<sup>22</sup> have shown us that an injection of parathormone in any dosage results in the following consecutive changes—increased urinary excretion of phosphorus, diminished blood phosphorus content, increased serum calcium content, and an increased urinary excretion of calcium, the net result being a tendency toward the production of a negative mineral balance. It has not been definitely decided that the fall in blood phosphorus actually precedes the rise in serum calcium, but the increased excretion of phosphorus seems to be the primary change and the hypercalcemia may well be a secondary compensatory phenomenon. At any rate, this hormone always causes a negative calcium and phosphorus balance at the expense of the bones, a fact hardly compatible at first glance with the increased mineral retention known to occur after therapeutic doses of vitamin D<sup>23</sup>. While it is true that excessive doses of this vitamin produce the same chemical changes that parathormone does, the amount of viosterol necessary to cause this reversal of action is so tremendous<sup>24, 25</sup> that the ensuing metabolic changes can hardly be compared to those seen in the clinic.

If, therefore, one is to postulate that vitamin D acts by stimulation of the parathyroid glands as Blunt and Cowan<sup>12</sup>, Hess and Lewis<sup>26</sup> and Greenwald and Gross<sup>27</sup> have done, one must first reconcile the opposing facts that an organism given parathormone loses minerals while one given viosterol in therapeutic doses usually retains them. This Greenwald<sup>27</sup> has done by assum-

ing that an organism, suddenly presented with an excess of available calcium from the reservoir in his bones through the action of viosterol, will retain the excess if he needs it (pregnancy, lactation) and thus exhibit a positive balance, whereas he will reject it if the demand is not great. If this assumption is true, it would appear that parathormone should be as good an antirachitic agent as viosterol, which it is not, and furthermore, that normal adults should respond to viosterol by increased mineral excretion, which they have not been shown to do. That this theory is not entirely satisfactory is evident from the opinion of Shohl<sup>27</sup> that the retention of calcium and phosphorus is determined solely by the amounts of these substances in the diet and that vitamin D regulates the intermediary metabolism "the dissolution and deposition of the bone salts." Wilder<sup>28</sup> too, in suggesting that rickets may be an expression of hyperparathyroidism, is driven to the opposite conclusion that viosterol works by inhibiting parathyroid activity.

Many scattered observations, however, attest to the fact that there must be some sort of intimate relationship between vitamin D and the parathyroid hormone. The following experiment of Hess has been widely quoted<sup>29</sup> — viosterol given to a normal monkey on a low calcium diet raised the serum calcium effectively, but after parathyroidectomy failed to do so. Nonidez and Gould<sup>30</sup> noted that the parathyroid glands became enlarged when they were kept in contact with ultraviolet light and a vitamin D poor diet. It is also of interest to observe that Hess<sup>31</sup> found that the shorter waves

lengths of sunlight chicks developed not only unmistakable hyperemia and hyperplasia, but degenerative lesions of a cystic nature in the parathyroid glands, and that these changes were considerably modified by the addition of small amounts of cod liver oil to the diet. Grant and Gates<sup>31</sup> on the other hand, had previously produced parathyroid hyperplasia by stimulating rabbits with ultraviolet light and whether these experiments contradict each other or whether the lesions were essentially different in nature is difficult to say, as the different species of animals may have been an interfering factor. It would appear, however, that they are open to almost any interpretation. Pappenheimer and Minor<sup>32</sup> called attention to the high incidence of parathyroid hyperplasia in human rickets and thus confirmed Erdheim's original observation with regard to the same phenomenon in experimental rickets<sup>33</sup>. Bauer, Albright and Aub<sup>34</sup> and Barr and Bulger<sup>35</sup> have collected all the available case reports of significant enlargement of the parathyroid glands, 60% of which, according to the latter authors, have been associated with obvious bone disease, usually osteitis fibrosa cystica, rickets or osteomalacia. While von Recklinghausen's disease has not yet been classed among those due to dietary deficiencies, Wilder<sup>36</sup> reported partial success in treating a case of this diffuse form of cystic osteitis with ultraviolet light and a diet rich in vitamin D.

In considering a possible interpretation for such observations as these, one meets a paucity of controlled experiments which might serve to answer two important questions — can vitamin

D increase mineral retention in the absence of normally functioning parathyroid glands, and, conversely, what are the effects of parathormone when given to an animal deprived of vitamin D? In an interesting paper Morgan and Garrison<sup>38</sup> call attention to these gaps in our knowledge and present experimental data which help to answer the second query. They show that in 11 young dogs fed a diet containing a normal amount of calcium and an insufficient quantity of phosphorus, but free from vitamin D, parathormone caused little response whether rickets was present or not, but that similar dogs, given viosterol also, showed an abnormally high response to parathyroid extract. They, therefore, conclude that vitamin D intensifies the activity of the parathyroid hormone, possibly by making it less easy for calcium or phosphorus or both to be excreted into the colon, and that viosterol should probably not be used in the treatment of hyperparathyroidism. Their data on total metabolic changes have not yet been published but will, it is hoped, shed light on this puzzling question of why an agent like viosterol which is known to increase mineral retention under the precise conditions of their experiment, should not be used to check the demineralizing process of hyperparathyroidism. Such clinical results as Wilder's<sup>8</sup> lead one to believe that it may actually be beneficial.

Data pertaining to the first question are considered experimentally by Greenwald and Gross.<sup>7</sup> It would seem an easy matter to remove the parathyroids from animals and then to observe the effects of vitamin D therapy, but those who have attempted to con-

trol parathyroid tetany by this means report contradictory results. Jones<sup>37</sup> found that cod liver oil given preoperatively to parathyroidectomized dogs usually prevented tetany, and has recently reported<sup>38</sup> that irradiated ergosterol also will not only prevent tetany under similar circumstances, but will produce hypercalcemia if given postoperatively. He used this drug in daily doses of 50 mg, however, which would imply that adult humans might require something over 100 c c of the usual commercial preparations daily, an absolutely prohibitive amount. Brougher, too,<sup>39</sup> found that the decline in serum calcium and the onset of symptoms were delayed and less severe if cod liver oil was given even postoperatively, later<sup>40</sup> he concluded that irradiated ergosterol afforded similar protection. Liu<sup>14</sup> however, got no results in a case of idiopathic hypoparathyroidism with cod liver oil, and Urechia and Popoviciu<sup>11</sup> as well as Greenwald and Gross<sup>7</sup> failed experimentally with viosterol, the latter even when large amounts of calcium were used. These authors point out the technical difficulty of removing all parathyroid tissue, and harmonize these conflicting results by predicating that residual parathyroid tissue, stimulated by vitamin D, will sometimes be sufficient to prevent tetany. If this theory is correct, it is easy to see that those cases of parathyroid tetany with a relatively large amount of residual parathyroid tissue will respond to treatment with viosterol, while those more severe cases in which the amount of functioning glandular tissue is presumably already working to full capacity will not

Obviously, then, neither theory is supported by decisive evidence and very likely, as our knowledge increases, it will be found that neither one is wholly true. The chief objection to the theory that vitamin D increases calcium absorption from the intestinal tract is that it is not proved, it rests upon chemical possibilities. The second theory is perhaps more attractive because of the undoubted relationship that exists between the parathyroid glands and certain bone diseases, but there are inconsistencies that prevent its ready acceptance. If the vitamin serves only to stimulate the parathyroids to greater secretory activity, it is fair to assume that parathormone should possess

for instance, to try to check the negative calcium balance of hyperparathyroidism with viosterol, but hesitates to do so with the theory in mind that the patient might be made worse by thus stimulating the parathyroids to even greater activity. Conversely, since a tetanic organism is already in positive mineral balance, it might be supposed that viosterol would make the situation the more acute by increasing the retention further, although advocates of the hormone-vitamin theory would probably anticipate benefit from stimulation of residual gland tissue. Certainly, more data are urgently needed.

#### CASE REPORT

D increase mineral retention in the absence of normally functioning parathyroid glands, and, conversely, what are the effects of parathormone when given to an animal deprived of vitamin D? In an interesting paper Morgan and Garrison<sup>36</sup> call attention to these gaps in our knowledge and present experimental data which help to answer the second query. They show that in 11 young dogs fed a diet containing a normal amount of calcium and an insufficient quantity of phosphorus, but free from vitamin D, parathormone caused little response whether rickets was present or not, but that similar dogs, given viosterol also, showed an abnormally high response to parathyroid extract. They, therefore, conclude that vitamin D intensifies the activity of the parathyroid hormone, possibly by making it less easy for calcium or phosphorus or both to be excreted into the colon, and that viosterol should probably not be used in the treatment of hyperparathyroidism. Their data on total metabolic changes have not yet been published but will, it is hoped, shed light on this puzzling question of why an agent like viosterol, which is known to increase mineral retention under the precise conditions of their experiment, should not be used to check the demineralizing process of hyperparathyroidism. Such clinical results as Wilder's<sup>37</sup> lead one to believe that it may actually be beneficial.

Data pertaining to the first question are considered experimentally by Greenwald and Gross.<sup>38</sup> It would seem an easy matter to remove the parathyroids from animals and then to observe the effects of vitamin D therapy, but those who have attempted to con-

trol parathyroid tetany by this means report contradictory results. Jones<sup>37</sup> found that cod liver oil given preoperatively to parathyroidectomized dogs usually prevented tetany, and has recently reported<sup>38</sup> that irradiated ergosterol also will not only prevent tetany under similar circumstances, but will produce hypercalcemia if given postoperatively. He used this drug in daily doses of 50 mg, however, which would imply that adult humans might require something over 100 c c of the usual commercial preparations daily, an absolutely prohibitive amount. Brougher, too,<sup>39</sup> found that the decline in serum calcium and the onset of symptoms were delayed and less severe if cod liver oil was given even postoperatively, later<sup>40</sup> he concluded that irradiated ergosterol afforded similar protection. Liu<sup>14</sup> however, got no results in a case of idiopathic hypoparathyroidism with cod liver oil, and Urechia and Popoviciu<sup>11</sup> as well as Greenwald and Gross<sup>27</sup> failed experimentally with viosterol, the latter even when large amounts of calcium were used. These authors point out the technical difficulty of removing all parathyroid tissue, and harmonize these conflicting results by predicating that residual parathyroid tissue, stimulated by vitamin D, will sometimes be sufficient to prevent tetany. If this theory is correct, it is easy to see that those cases of parathyroid tetany with a relatively large amount of residual parathyroid tissue will respond to treatment with viosterol, while those more severe cases in which the amount of functioning glandular tissue is presumably already working to full capacity will not

Obviously, then, neither theory is supported by decisive evidence and very likely, as our knowledge increases, it will be found that neither one is wholly true. The chief objection to the theory that vitamin D increases calcium absorption from the intestinal tract is that it is not proved, it rests upon chemical possibilities. The second theory is perhaps more attractive because of the undoubted relationship that exists between the parathyroid glands and certain bone diseases, but there are inconsistencies that prevent its ready acceptance. If the vitamin serves only to stimulate the parathyroids to greater secretory activity it is fair to assume that parathormone should possess antirachitic powers also, properties which have never been claimed for it. Furthermore if it is agreed that viosterol leads to increased mineral retention in young animals or in those whose demand for calcium is greater than normal it should follow that parathormone will also cause a negative calcium balance to become normal under these conditions. The opposing effects upon mineral balance of parathormone and irradiated ergosterol are difficult to reconcile on the theoretical assumption of a given animal's need for calcium. The complicating factors are many and intricate and one feels that until more is known about phosphorus metabolism particularly such theories as these will remain only theories. In the meantime there are apparently no other more suitable hypotheses to work on.

When one attempts to apply all this to the treatment of disturbances of mineral metabolism the confusion becomes all the greater. One is tempted

for instance, to try to check the negative calcium balance of hyperparathyroidism with viosterol, but hesitates to do so with the theory in mind that the patient might be made worse by thus stimulating the parathyroids to even greater activity. Conversely since a tetanic organism is already in positive mineral balance, it might be supposed that viosterol would make the situation the more acute by increasing the retention further although advocates of the hormone-vitamin theory would probably anticipate benefit from stimulation of residual gland tissue. Certainly, more data are urgently needed.

#### CASE REPORT

The admission of a woman to the hospital wards gave us an opportunity to try viosterol therapy and to get what information we could which might support one theory or the other. Unfortunately, the mental condition of the patient was such that it was impossible to obtain anything like complete metabolic studies so that our data are limited to blood studies, the value of which is admittedly limited.

Mrs. L. P., a 29 year old Scandinavian housewife, was admitted to the medical wards of the hospital of the University of Michigan in March, 1930, because of repeated convulsions. Lingual difficulties and the low mental status of the patient precluded a full and accurate history, but it was learned that 12 years previously, she had undergone an operation for goitre in another city. Two weeks after leaving the hospital there, she had an attack of generalized muscular rigidity accompanied by coma, cyanosis, foaming at the mouth biting of the tongue, and urinary incontinence. Since then, she had had countless numbers of similar episodes. They came on without aura or known cause and usually lasted five or ten minutes, having been particularly frequent during the menstrual periods when she had had as many as seven in one day. Her husband denied ever having noticed that her hands assumed a position that might be in-



terpreted as carpo-pedal spasm or that she had ever cried out in a manner to suggest laryngospasm. Following such an attack, she always felt weak, but had no pain or headache.

During this period of 12 years, she bore two children without difficulty, during the pregnancies and succeeding periods of lactation she was, curiously enough, entirely free from attacks. Her finger nails are stated to have fallen off five times since her operation, and she had a great deal of trouble with her teeth which had become very soft. For the past three or four years, her vision had failed rapidly until, on admission, she was barely able to distinguish one object from another. No parathesias were complained of.

Her past history was apparently uneventful, except for influenza in 1918 and pneumonia in 1929. She had had a spontaneous miscarriage in 1927. She and her husband denied any fits or mental trouble prior to her operation for goitre, but a family friend told us that the patient had often had periods of irresponsibility since girlhood. The family history was unimportant.

Physical examination revealed the following important items—(1) Each eye showed many radiating lenticular opacities of the mossy type, most marked in the nuclear regions, (2) dental caries of an unusually severe degree, (3) a thyroidectomy scar of the usual collar type, (4) marked dystrophy of the finger nails characterized by deep transverse folds and extreme brittleness, (5) a strongly positive Chvostek's sign and (6) an easily demonstrable Trousseau phenomenon.

Laboratory studies revealed a slight secondary anemia, the erythrocytes being 4,190,000, the hemoglobin (Sahli) 73%, the leucocytes 7,050 and the differential smear entirely normal. The serum calcium was 7.9 mg per 100 cc serum. The blood inorganic phosphates were 5.8 mg per 100 cc plasma. The fasting blood sugar was 102 mg per 100 cc. The routine diagnostic blood Kahn tests were repeatedly 3 or 4 plus, but the spinal fluid was entirely normal. The basal metabolic rate was plus 15%. The urine and stools were both normal. X-ray plates of the skull and long bones were negative and revealed no striking change in bone density.

Stimulation of the ulnar nerve resulted in a cathodal opening contraction with 2 milliamperes of galvanic current.

The diagnosis was latent parathyroid tetany, epilepsy of the grand mal type and latent syphilis. The character of the convulsions together with the striking fact that the periods of pregnancy and lactation represented the only intervals of freedom from them convinced us that they bore no relation to the parathyroid deficiency, although Gibson<sup>42</sup> quotes Redlich as having collected 72 cases in which epilepsy accompanied or followed tetany. There were no clinical signs of active lues, and we felt that syphilitic epilepsy in the face of a normal spinal fluid was a remote possibility.

*Clinical Course*—The patient was almost immediately given 1 cc of viosterol (Parke, Davis and Company) morning and night. This preparation is valued at 100 D, and is stated to contain about 0.7 mg of irradiated ergosterol per cc. No other medication was given and she received the usual ward diet without restrictions. After ten days of this regime, her serum calcium had fallen from 7.8 to 6.1 mg per 100 c c, and at the same time the inorganic phosphates of the blood had risen from 6.0 to 6.9 mg per 100 c c. These events did not seem to indicate increased calcium absorption and she maintained the signs of latent tetany which she presented on admission. An attempt was then made to study her mineral metabolism in accordance with the methods outlined by Aub<sup>43</sup>. A diet was kindly prepared by Miss Ina Stevenson, hospital dietitian, which contained an average daily ra-

tion of 0.1 gm of calcium, 0.5 gm of phosphorus, 2-3 gm of NaCl, sufficient protein to keep the patient in nitrogen equilibrium and enough calories to prevent loss of weight. At this point, however, seizures became so frequent and the patient so completely out of hand that all attempts to collect excreta or to measure accurately food consumption became out of the question. The low calcium diet was continued, however, since it allowed a more accurate estimation of calcium intake, the patient never took more and usually received less than the calculated amount.

This psychosis was classifiable only as a mixed psychogenic reaction. She rather rapidly developed a complete disorientation accompanied by hallucinations, great apprehension and periods of hypomania alternating with short intervals during which she would lie passively in bed with her eyes fixed to the ceiling, but in constant lateral nystagmus. During these quiet periods, she would cooperate well and insist that she felt entirely comfortable. The reflexes were equally sluggish throughout and no pathological ones were obtained. She was completely incontinent of bladder and bowel. Seizures were frequent, but neither the number of convulsions nor the degree of psychosis bore any apparent relation to the level of serum calcium. Fünfgeld,<sup>41</sup> however, has described definite tetany psychoses.

In spite of the lowered calcium intake, no further change of any magnitude took place in the blood calcium or phosphorus levels during the next two weeks. In accordance with the suggestion of Dr. Walter Bauer, who was

kind enough to see this patient with us, the following study of calcium absorption was made. The patient, having been without viosterol or other medication for two weeks, and having been on the low calcium diet for one week, was given by mouth 10 gm of calcium-gluconate, a compound containing about 10% calcium and free from disturbing acid-producing properties. The fasting serum calcium was determined beforehand and deviations from it followed by withdrawing blood every hour for six hours after ingestion of the gluconate, and then at 9, 12 and 24 hours. Later, viosterol was administered under the same conditions in daily doses of 20 cc for two weeks, and the same test repeated. The two absorption curves are shown in Figure 1\*.

We have only one conclusion to draw from these two curves and that is that, in this instance, large doses of viosterol did not increase the absorption of calcium from the intestinal tract. It will be noted that after the administration of viosterol, the initial level of calcium is slightly elevated. That this probably does not mean increased calcium absorption is shown by the absence of any post-ingestion rise, it might be explained on the basis of parathyroid stimulation and doubtless this woman had residual gland tissue, else her tetany would have been more manifest. We have no explanation for the absence of the post-ab-

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\*Miss Mary L. Stanley very kindly performed all blood chemical determinations. The Clark-Collip modification of the Kramer-Tisdall method was used for estimating the serum calcium, and the Fiske-Subbarow method for blood inorganic phosphate.

sorptive rise in the second instance, but feel that it is an indication that the vitamin D medication did not augment mineral absorption in the intestinal tract

At this point, because of the patient's mental condition, she was transferred to another institution where it is hoped that she can be followed. Before discharge, her blood calcium and phosphorus levels were restored to their normal levels by injections of parathormone and the signs of increased nerve irritability disappeared for the first time. Since she was a relatively mild case of tetany it was thought that she would probably do well on large doses of calcium by mouth, however, so that parathormone was discontinued on discharge, and the patient equipped with calcium lactate. The

slight rise in serum level produced by viosterol in the second test prompted us to prescribe this substitute also

CONCLUSION

(1) A case of parathyroid tetany associated with epilepsy and acute psychosis is reported

(2) The theories of the action of irradiated ergosterol are briefly described and evidence is presented to show that one of them which supposes that vitamin D increases calcium absorption from the intestinal tract is not supported

(3) The mechanism by which irradiated ergosterol acts is not known. It seems highly improbable that it stimulates the parathyroid glands to increased secretory activity

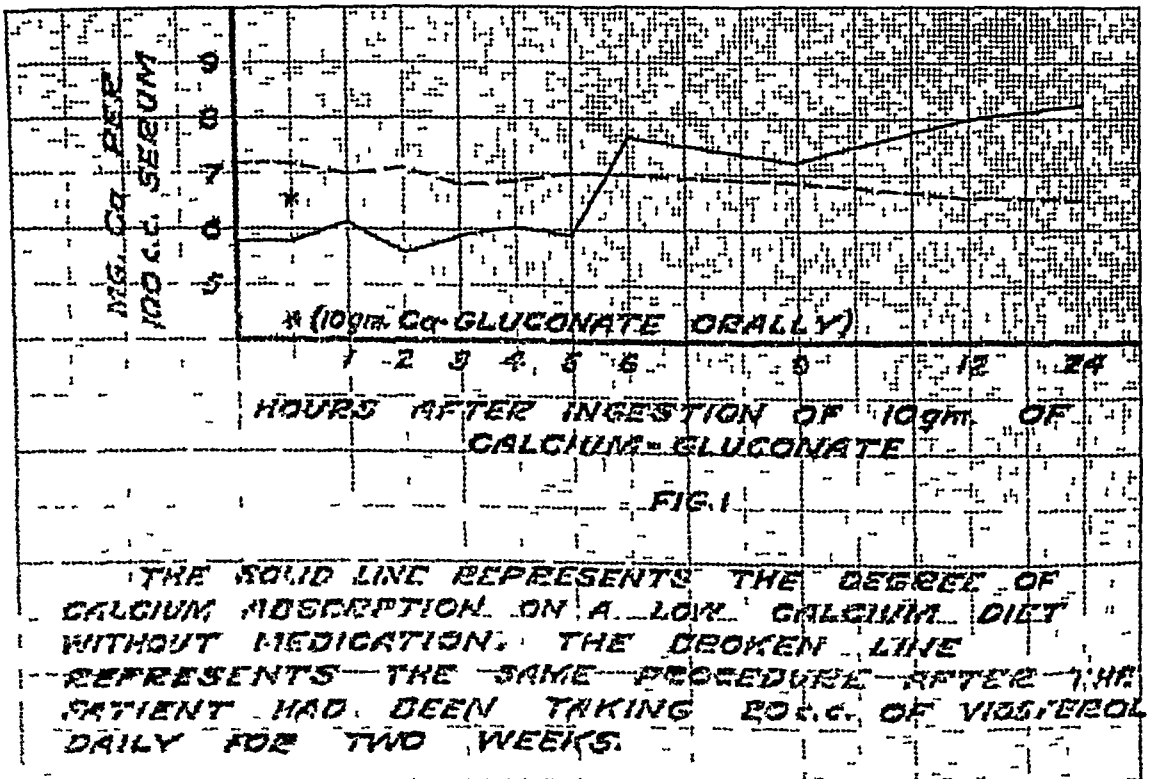


FIG. 1

(4) Large doses of viosterol alone are insufficient treatment for parathyroid tetany and it is thought that even if it be combined with calcium therapy the viosterol is an unimportant factor

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# Recovery from Streptococcus Meningitis\*

## Report of a Case and an Analysis of Reported Cures.

By LESTER ROSENBERG, M. D. AND HAROLD W. NOTTLEY, M. D.,  
*Brooklyn, N. Y.*

IT requires no brief to substantiate the statement that streptococcus meningitis is ordinarily a fatal disease. Clinical contact with any type of suppurative meningitis, excepting perhaps the meningococcus, has taught us the gravity of this type of illness. The mortality for the streptococcus form is exceedingly high and cases of recovery, although they do occur from time to time, are rare enough to be always worthy of interest.

We present a case of recovery and a study of reported cases of cure. Although we have carefully attempted to review all the pertinent literature, we cannot help but feel that possibly additional cases of recovery have been overlooked. Numerous references have been studied in which only diplococci have been reported, with no further description of the organism found. Unless specified to the contrary, we have assumed the bacteria to be the meningococcus or probably the pneumococcus. Such cases have, of course, been omitted from further consideration. By far the greatest amount of work on the subject of purulent meningitis has been

done by otologists. Comprehensive studies are found in the literature of almost all countries, particularly in Germany.

We believe that any additional instance of a case which survives streptococcus meningitis should serve to stimulate a careful study of the surrounding circumstances. The therapy employed should be analyzed with the view that a rational empiric, if not a specific, therapy may be ultimately evolved. Particularly is recovery rare when, as in our case, the meningitis is unrelated to any remediable source of infection.

### CASE REPORT

M. B., aged 6 years, was admitted to the Brooklyn Hospital February 23, 1929, complaining of backache, fever, and pain in the back of the neck. Six weeks prior to admission she had had a slight cold with sore throat, accompanied at the time by chills, fever and vomiting. The vomiting was described as projectile in nature. For four weeks the condition had abated little, there were still recurrent chills, fever, headache and vomiting, and two weeks before admission the child developed a stiff neck with constant pain in the back.

*Precious History.* The patient's general health had been good. She had measles at the age of two, otherwise no infectious or contagious diseases. The father, mother and five other children were living and well.

\*From the Pediatric Service of the Brooklyn Hospital, Brooklyn, N. Y., Dr. A. D. Scott, Director.

*Physical Examination* Showed a fairly well developed and well nourished girl, lying in bed, acutely ill, crying and complaining constantly of headache and pain in the back.

There was marked rigidity of the neck to a degree that no forward bending was at all possible. The pupils were equal, reacted to light and accommodation, there was no nystagmus or strabismus. The knee-jerks were hyperactive. There was no Babinski sign or Gordon or Oppenheim. No ankle clonus. The Brudzinski sign was positive. Kernig's sign was bilaterally present.

There was no mastoid tenderness, both ear drums were normal. There was herpes on the lips, the tongue was coated, the pharynx was red and injected, the tonsils were small, cryptic and infected. Slight cervical lymph node enlargement was present. There was no impairment of resonance in the lungs, breathing was vesicular, no râles were heard. This heart was normal, the rate rapid but regular, no murmurs were present. The abdomen was slightly distended, there was no tenderness and no masses were felt. There was marked anterior bowing of both tibiae, with suggestive sabre shaped surfaces.

Urine examination showed a heavy trace of albumin, but no sugar. Many pus cells were present microscopically. The white blood cell count was 20,000, with 68 per cent polymorphonuclears, 32 per cent lymphocytes, red blood cells 4,350,000, hemoglobin 68 per cent.

*February 23rd* (day of admission) Lumbar puncture was done and 50 cc of cloudy fluid obtained, showing a cell count of 2435 per cmm, almost all polynuclear cells, globulin two plus (++) , sugar slightly decreased. No organisms were seen on smear. 10 cc of a concentrated preparation of a commercial antimeningococcus serum were given.

*February 24th* Lumbar tap was repeated twice during the day with the removal of 40 cc at 10 A M and 52 cc at 6 P M of cloudy spinal fluid. 35 cc and 38 cc of antimeningococcus serum were injected following each tap, respectively. No organisms were demonstrable on smear. The patient's condition was poor, she cried frequently during the day, was restless, irritable, and vomited once, she took fluids very poorly.

*February 25th* The child was extremely restless, her condition appeared to be getting worse. Three lumbar punctures were done this day. At 2 A M, 50 cc of cloudy fluid were removed and 35 cc of antimeningococcus serum were given. At 4 P M, 40 cc were removed and 20 cc of serum given. At midnight, 35 cc were removed and 20 cc of serum given. No organisms were demonstrable on smear. The cultures were still sterile.

*February 26th* The patient had become very restless and cried out a great deal. The opisthotonos had become marked. In an effort to relieve pressure, three lumbar punctures were done again on this day. At 10 A M, 30 cc were removed and 20 cc of serum given. At 5 P M, 23 cc were removed and 20 cc of serum given. At midnight 42 cc were removed and 20 cc of serum given.

*February 27th* The patient appeared to be a little more quiet, although still complaining of severe pain in the head and in the legs. At 8 A M, 20 cc of spinal fluid were removed and 15 cc of antimeningococcus serum given. A long chain streptococcus was demonstrated in direct smear of this fluid, and in the afternoon the culture of the second day's fluid was reported as containing a partial hemolytic streptococcus. At 9 P M, 30 cc of turbid spinal fluid were removed and 15 cc of a commercial antistreptococcus serum given.

*February 28th* There was little change in the extreme condition of the child. Opisthotonos was marked. Feeding was done with difficulty. A hemorrhagic rash was present on the body. At 9 A M, 45 cc of turbid spinal fluid were removed and 18 cc of antistreptococcus serum injected. At 7 P M, 30 cc of turbid spinal fluid were removed and, before injecting 15 cc of antistreptococcus serum, the canal was irrigated with about 20 cc of 1-4000 aqueous solution of neutral acriflavine.

*March 1st* Restlessness continued, the head was markedly retracted. Two lumbar punctures were done. At 9 A M, 45 cc of turbid spinal fluid were removed, the canal irrigated with 1-4000 acriflavine solution, and 10 cc of antistreptococcus given. A long chain streptococcus was present in the smear. At 10 P M, 25 cc of turbid spinal fluid

were removed and the spinal canal irrigated with 1-4000 acriflavine, no antistreptococcus serum was given

*March 2nd* The child's condition was worse. She had an involuntary bowel movement. Her head was markedly retracted. Two lumbar punctures were done, one at 9 A M with the removal of 35 cc of cloudy fluid, and another at 10 P M, when 25 cc were taken off. On both occasions the canal was irrigated with 1-4000 acriflavine and 10 cc of antistreptococcus serum were given only after the morning puncture.

*March 3rd* The patient's condition was little changed, she swallowed with difficulty. At 11 A M, 36 cc of cloudy spinal fluid were removed, the canal irrigated with acriflavine, and 10 cc of antistreptococcus serum given. The cell count was 4300 per cmm, almost all polynuclears.

*March 4th* There was some improvement in the patient's general condition. Her head was slightly less retracted. The blood culture was sterile. At 9 A M, 20 cc of cloudy fluid were removed and the canal irrigated with acriflavine solution, no serum was given. The cell count was 1200 per cmm.

*March 5th* There was little change in the patient's condition, she was still having difficulty in swallowing. Only 3 cc of turbid spinal fluid could be obtained on puncture. Irrigation of the canal, however, was possible and, after 12 cc flowed in by gravity, 24 cc of yellowish turbid fluid were removed. Apparently a block had been broken through. No serum was given.

*March 6th* The patient's condition was better. She was able to swallow. No fluid could be obtained in the morning lumbar puncture but at 7 P M about 1 cc of yellowish but clear fluid was removed. Again the canal was irrigated with acriflavine solution. No serum was given. The cell count was not done.

*March 7th* The patient was very restless and fidgeting continually. On lumbar puncture only 2 cc of clear yellowish fluid could be obtained; it contained 25 cells per cmm. Efforts to relieve pressure by the lumbar puncture and the occurrence of extreme rigidity of the spine made removal of fluid by lumbar puncture advisable. Under pres-

oxygen-ether anaesthesia, 33 cc of clear watery fluid were obtained, containing only 55 cells per cmm, chiefly polynuclears. 10 cc of another commercial brand of antistreptococcus serum were given. The spinal fluid gave a normal reduction for sugar.

*March 8th* Patient's condition was much improved, she slept well during the night. Only 2 cc of fluid could be obtained by the lumbar route, but it was watery clear. A normal reduction test for sugar was present.

From this time on, the child's general condition improved, though slight temperature persisted. She was mentally brighter, answered questions intelligently, but the retraction of the neck persisted. No further lumbar taps were done.

*March 12th* The blood Wassermann was negative.

*March 16th* The patient was greatly improved and was put out on the porch, was able to take solid food. The retraction of the neck was improved, her temperature was normal.

*March 25th* Patient was able to sit up in bed. Her neck was no longer stiff. She looked well, though drawn and somewhat pale.

*March 27th* She was out of bed for the first time in a wheel chair.

*April 1st* Patient was up and about. There was no impairment of her gait, no residual disturbances in the central nervous system were apparent. Her recovery appeared excellent.

*April 11th* Throat culture showed long chain streptococcus.

*April 12th* The blood Wassermann was three plus.

*April 19th* The blood Wassermann was two plus.

Just prior to discharge, examination revealed the following:

The cycloids showed no pathological changes. Normal vision was present in both eyes. The intradermal tuberculin test (1/10 mm) was negative. X-ray examination of the teeth showed no abscesses present, though dental caries was present in the upper molars. The nasal sinuses were clear, the mastoid cells were not clear on either side, perhaps due to lack of development, though more



FIG 1 Photograph taken March 5, 1929, showing extreme opisthotonus. A hemorrhagic rash is visible on trunk and extremities.



differentiation at her age would be expected

*Neurological Examination* She understood and performed all tests well. The cranial nerves were normal. The pupils reacted to light and accommodation, fundi were normal. The reflexes were normal. There was no Kernig and no rigidity of the neck. There was definite tremulousness of the muscles of the lower extremities, particularly when the leg performed gross movements. No mental impairment was evident. The Binet-Simon and Pintner-Cunningham tests were done, both averaged her mental age at about 7 years, which was her approximate chronological age.

*April 17th* The patient was discharged, apparently entirely well, 54 days after admission.

#### SUMMARY

Streptococcus (partial hemolyticus) meningitis with complete recovery in a girl age 6. The onset followed an acute sore throat and upper respiratory infection, and the illness ran a long course. The treatment consisted of repeated lumbar punctures and spinal canal irrigations with 1-4000 neutral acriflavine aqueous solution and antistreptococcus serum injections. Cisterna puncture became necessary on one occasion, when block had apparently developed. Recovery was slow but complete.

#### COMMENT

The significance of the positive blood Wassermann reaction on two occasions is difficult to determine. Aside from the suggestive sabre-shaped tibiae, there were no signs of lues. The serological findings will bear re-checking and specific treatment will be instituted if positive results are obtained. The relation of the possible presence of lues to the meningitis, however, seems purely incidental, but it is of importance when one is trying to estimate

and correlate the factors which may influence the prognosis.

The use at first of antimeningococcus serum, before any organism was isolated, followed later by specific antistreptococcus serum and still later by acriflavine aqueous solution (1-4000) canal irrigations, makes it difficult to determine with any degree of accuracy the value of any or all of the therapeutic agents employed. It does not seem likely that the antimeningococcus serum could have been of benefit, except perhaps as a foreign protein. Clinically at least, no improvement was noted during the period when antimeningococcus serum was used, actually, the patient had grown worse. No improvement was noted with the antistreptococcus serum until the acriflavine irrigation was instituted, at first in combination with the serum and later alone. Whether recovery, when it occurs, proceeds spontaneously and irrespective of treatment, there is no way of judging, but, in our own case at least, clinical improvement began and progressed under a combination at first of antistreptococcus serum injections and neutral acriflavine solution irrigations, and later with acriflavine irrigations alone.

#### SUMMARY OF REPORTED CASES

Despite the rarity of recovery, we have been able to gather from the literature a record of forty other instances of recovery from streptococcus meningitis.

*Historical* Though recent writings credit the first reported instance of recovery to Alexander, in 1908, Schenke and Strat reported a case in 1901;

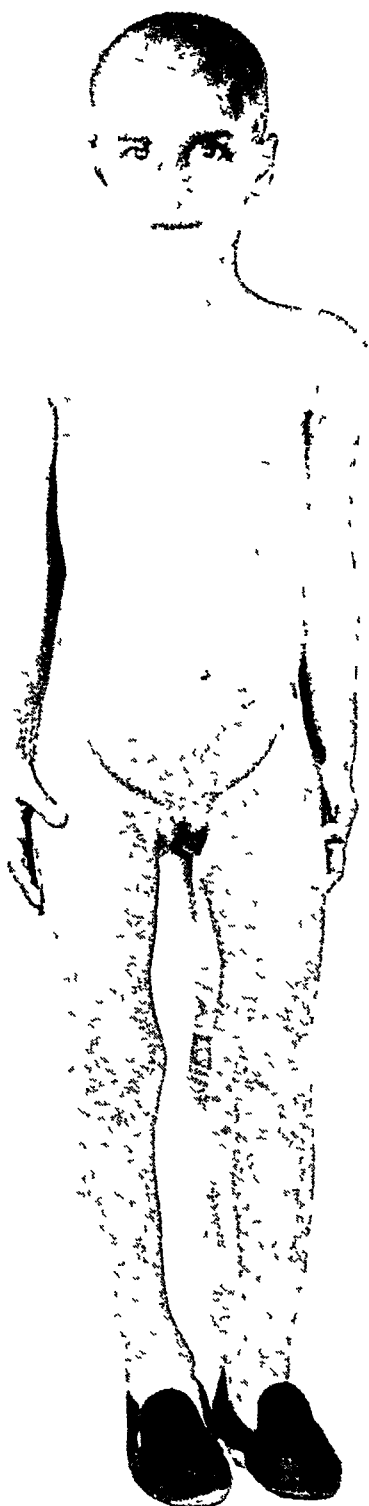


FIG 2

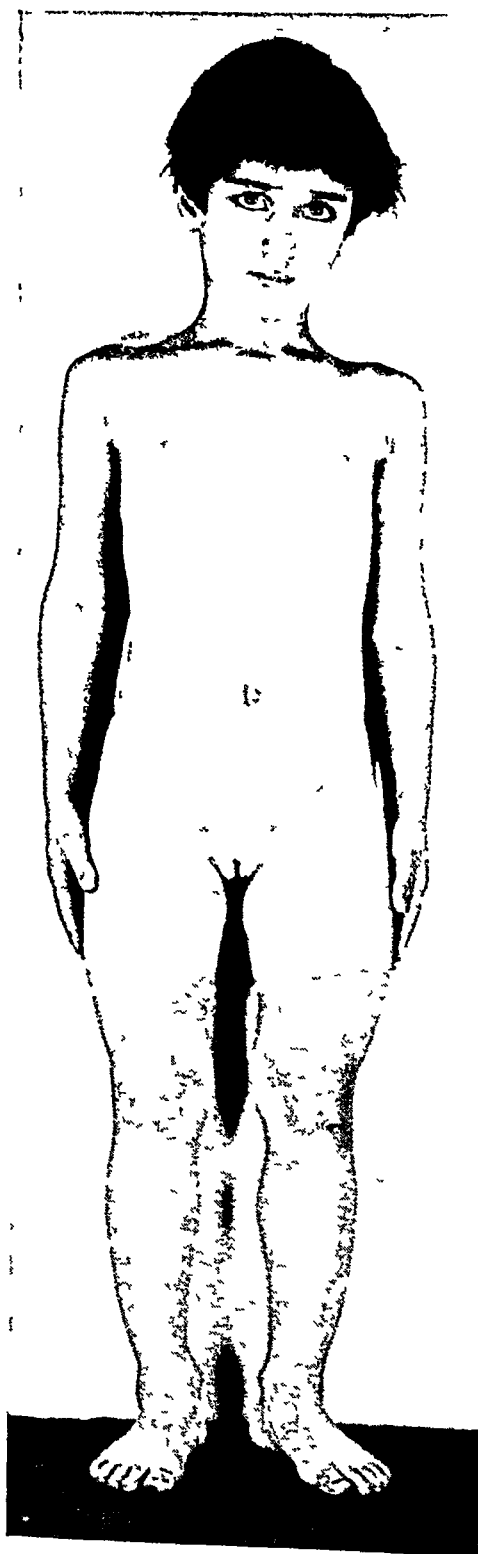


FIG 3

FIG 2 On discharge from the hospital, April 17, 1929

FIG 3 Appearance of patient, September 26, 1929

Schulze published one in 1903, Gruening told briefly of a case before the New York Otological Society on March 22, 1904 and Voss published one in 1905. In the case published by Schenke and Streit, however, it must be said that only one streptococcus was seen on smear, the spinal fluid, however, was turbid. Thereafter came Alexander, in 1908, with two cases, Netter with one in 1909, one by Graef and Wynkoop and one by Mygind in 1910, Tedesco and Ohnacker each recorded one case in 1911. From 1911 to 1920 inclusive, 13 cases were reported, and from 1921 to the present there were 17 cases, including our own.

*Age* Of the 41 cases, the age is not given in only one instance.

Under 2 years	1
2 years	1
5 years	2
6 years	2
7 years	4
8 years	2
10 years	3
11 years	1
12 years	3
13-20 years	6
21-25 years	5
26-30 years	2
31-35 years	2
36-40 years	2
41-45 years	1
46-50 years	2
65 years	1

Fifteen, or 37.5 per cent, occurred in the first decade of life, ten, or 25.0 per cent in the second decade, seven, or 17.5 per cent in the third decade, four, or 10.0 per cent, in the fourth decade and four, or 10.0 per cent, after the age of 40.

One can only postulate on the reasons for the high incidence in early life. One factor that would seem to suggest

itself is the greater frequency of otitic infections during this period. Actually, otitis media, as will be shown shortly, was the inciting cause in 66.6 per cent of all cases. After the age of thirty, recovery is relatively rare, but, lacking statistics of occurrence in a large series of cases, it is of little value to attempt any conclusions as to percentage mortality for any given age group.

*Sex* In one instance the sex is not stated. Of the remaining cases, twenty-three were males and seventeen females.

	Male	Female
Under 2 years	1	0
2-10 years	4	10
11-20 years	7	3
21-30 years	5	2
31-40 years	3	0
41-50 years	2	2
Above 50 years	1	0

Though the general incidence is somewhat higher in males, it is striking that in the first decade there are twice as many females as males who recovered.

*Source of Infection* In twenty-eight, or 68.3 per cent of the cases, the source of infection was directly traceable to otitis media, rarely alone and most often in combination with mastoiditis. In one case (Alexander) the otitis was associated with an extradural abscess. In four instances (Voss, Neal and Jones, Ohnacker, Neal), the otitis followed upon scarlet fever, in two instances (Netter, Crockett) following measles. In Lang's case the scarlet fever was questionable, but an acute tonsillitis was present. One case followed upon brain abscess (Day), one after submucous nasal septum resection (Graef and Wynkoop), three occurred after trauma to the

Head (Dandy, Leighton and Pringle, McCarthy), one after trauma to the back (Barth), two were questionable in origin, the first (Patzig) having played football the previous evening, the second developing otitis media after the onset of the meningitis (Urbant-schitch). Two cases followed upon acute tonsillitis alone (Vining and Thompson, Rosenberg and Nottley), one occurred after removal of a cerebellopontine tumor (Dandy). In two instances (Tedesco, Weaver) no source of infection could be demonstrated.

*Organism* In some of the early cases the diagnosis rested on finding streptococci in the smear of the turbid spinal fluid, no culture being reported. These observations cannot have the finality that isolation of the organism on culture media necessarily imparts. Yet streptococci are so rare as contaminating organisms, that their presence in the smear alone is sufficient evidence, it would seem, to stamp the case as of streptococcic origin. In one instance (Schenke and Streit) only one organism was found in the smear.

The classification of organisms found is as follows:

Streptococcus	
(type not specified)	21
Streptococcus hemolyticus	10
Streptococcus hemolyticus	
(scarlet fever group)	1
Streptococcus pyogenes	4
Streptococcus viridans	4
Streptococcus mucosus	1

*Treatment* Only a casual study of the cases gathered here will suffice to disclose the varied method of treatment employed and to emphasize that

no successful specific procedure has yet been evolved.

In seven cases (Patzig, Netter, Schulze, Tedesco, Neal, Shaw, Acker) lumbar puncture alone was successful, and in one instance (Bowers) lumbar puncture and jugular ligation. Huenekens and Stoesser did a mastoidectomy and employed irrigation of the spinal canal with normal saline. McCarthy injected human serum intraspinally. Mastoidectomy and repeated lumbar puncture were successful in three cases (Bondy twice, Schenke and Streit). Watson-Williams employed intraspinal injections of a silver preparation (collosol argentum) after doing a mastoidectomy. In six instances mastoidectomy alone proved sufficient (Alexander, Askey, Scott, Mygind, Yergei and Voss), and in one instance labyrinthotomy (Bondy). Lumbar laminectomy and drainage were done in three cases that recovered, once by Barth and twice by Leighton and Pringle. McKenzie drained the spinal fluid by way of a wire drain in the internal ear and an incision in the cerebral dura. Alexander performed labyrinthotomy and drained cerebro-spinal fluid through the dura and also locally by way of the internal ear. Dandy on two occasions instituted surgical drainage through the cisterna magna, and Day drained the cerebral dura alone. Graef and Wynkoop were successful with autogenous streptococcus vaccine subcutaneously. Antistreptococcus serum was used either alone or in conjunction with other methods by Weaver, who gave antistreptococcus serum intraspinally, by Crockett and DuBois and Neal, who used antistreptococcus serum intraspinally and urotropin by

mouth, by Ohnacker, who performed mastoidectomy and made use of antistreptococcus serum intraspinally, by Urbantschitch, who followed Ohnacker's procedure, but also used urotropin intravenously, by Vining and Thompson, who employed antimeningococcus and antistreptococcus serum intraspinally, by Day, who gave antistreptococcus serum intraspinally and autogenous streptococcus vaccine subcutaneously, by Neal and Jones who used anti-scarlet serum intraspinally and, on one occasion, 3-4 cc of 1 per cent neutral acriflavine. On another occasion Neal used antibacterial and antitoxic serum (scarlet), prepared by the New York Department of Health, intraspinally and 5000 units once intravenously. Lang was successful using antimeningococcus serum at first and then antiscarlet serum intraspinally and intravenously. He also resorted to two blood transfusions. In our own case, antimeningococcus and antistreptococcus serum was used intraspinally, the latter in conjunction with irrigation of the canal with 1-4000 solution of neutral acriflavine.

*Comment.* Surely, when in forty-one definite cases of recovery so many different procedures are resorted to, it is not necessary to call attention to the absence of a specific treatment for streptococcus meningitis. To suggest that many of these cures are spontaneous and would have occurred regardless of treatment or sometimes in spite of it would not be at all original. Dandy, discussing his own cured cases, says, although the mortality is extremely high, spontaneous cures do occur, a fact which makes it open to

doubt whether many recoveries—including my own—have not really occurred in spite of, rather than because of, treatment. Indeed some forms of therapy are so vigorous and many so devoid of surgical and physiological reasoning that one is forced to the conclusion that actual damage has been added to very sensitive tissues which need all their strength to combat the infection."

Brieger produced experimental streptococcus meningitis in dogs and noted spontaneous recovery in four of fourteen cases which were untreated. Recovery also was spontaneous in one of three untreated cases in monkeys.

In the light of our own case and in the attempt to evolve a logical method of treatment, it is of more than usual interest to note the result of animal experimentation carried out by Kolmer, Rule and Madden. These authors have been successful in treating induced streptococcus meningitis in dogs with chemotherapy and serum therapy, employing antistreptococcus serum and gentian violet or neutral acriflavine by cerebral cisterna lumbar lavage. They noted the following: "Furthermore, there is no chemotherapeutic agent for streptococcus infections comparable to ethyl hydriocuprein hydrochloride for pneumococcus infections, although I believe that the addition of gentian violet or neutral acriflavine to antistreptococcus serum appreciably enhances its streptococidal activities." These writers have as yet had no success in human cases, but they add further: "A polyvalent antistreptococcus serum, therefore, should be employed and to each 25 cc one may add 1 cc. of a 1-100 solution of gentian vio-

let of acriflavine in sterile physiologic solution of sodium chloride. The mixture should be warmed before injection, or a 0.5 per cent solution of neutral acriflavine may be employed."

Enough successful work with acriflavine solution and antistreptococcus serum has, of course, not yet been reported. It would be presumptuous for us even to attempt to detail any method of treatment as having a greater likelihood of cure than another. Yet, on the basis of experimental data and of the successful outcome in our own case which seemed so nearly hopeless, we would like to see our method tried in other cases.

The routine resort to surgical interference and the expressed opinion that suppurative meningitis is as much a surgical condition as is suppurative peritonitis, we do not believe to be sound. Surgical removal of any offending focus, particularly in connection with demonstrated ear infection, should, on the other hand, by all means be done.

Should routine mastoidectomy be done in cases of streptococcus meningitis, even though the ear drums appear normal? Urbantschitch did this in his own case and advocates it as a necessary procedure in treatment of streptococcus mucosus meningitis, regardless of the normal appearance of the tympanic membrane. That this may apply in cases of streptococcus mucosus meningitis is possible. We do not believe it applicable to streptococcus meningitis in general. We cannot agree, too, that the early mastoidectomy in Urbantschitch's case was directly responsible

for the recovery. The bilateral mastoid operation was done on January 8th, yet the patient continued to have bouts of remittent fever and meningeal signs through the months of January, February, March, and part of April. In our own case of undemonstrable origin, we cannot see how mastoidectomy in the presence of normal drum membranes, which remained so throughout the course of the disease, could have served any useful purpose. On the other hand, it may have been productive of much harm.

The procedure of cerebellar decompression and drainage of the cisterna magna was employed in suppurative meningitis, but unsuccessfully in six cases by Haynes and Kopetzky. Day failed to get a cure with this procedure in nine cases. The latter author says that, though drainage of the cisterna magna hinders the development of a diffuse meningitis over the hemispheres and prevents the accumulation of pus in the pia arachnoid, it does not influence the progress of the infection at the base of the brain. It appears to have no effect on the accumulation of inflammatory exudate in the subdural spaces. Neal says that the results of operative procedures in general have been very discouraging.

#### INDEFINITE CASES NOT INCLUDED IN THE SERIES

For the sake of completeness, some indefinite cases not included in the group of recovered cases because of incomplete data or complicating factors must here be described.

Gleich reported a case in a male colored infant, aged two months, who developed a streptococcus meningitis and was treated by antimeningococcus and antiscarlatinal serum. Improvement followed. Yet, two and one-half months after the onset, streptococci were still demonstrable in the spinal fluid. Hydrocephalus developed and the infant, who never left the hospital, died at the age of seven months from broncho-pneumonia.

In Bryant's case the data are meagre. His patient was a man 22 years old with definite meningeal signs and in whom recovery ensued after decompression and mastoidectomy. No mention is made whether the organism was diagnosed on smear or culture, and the patient died after 188 days "from toxemia caused by repeated secondary infection of the decompression wound."

Gruening, discussing a paper before the New York Otological Society in 1904, "remembered a case of a boy whom he had operated on for brain abscess some five years ago. He was taken very ill with convulsions and stupor, with the discharge of a serous fluid from his ear. Lumbar puncture was performed and the fluid evacuated was distinctly turbid and contained streptococci. The case recovered." No other details are given.

In Ranney and Alford's case the culture of streptococci was made from spinal fluid discharging through the ear and not from fluid removed directly from the cerebro-spinal system. Bruger mentions two cases of recovery in streptococcus meningitis in which the organism was demonstrated in smears of the cerebro-spinal fluid, and Decker also reports, without de-

tailed description, a case of recovery from streptococcus meningitis. The organism was isolated on culture and demonstrated also on direct smear.

#### BACTERIA IN THE CEREBRO-SPINAL FLUID WITHOUT MENINGITIS?

In considering cases of recovery from purulent meningitis, it is well to consider for a moment that cases are recorded in the literature that showed organisms in the spinal fluid and yet revealed no meningeal involvement at autopsy. Heubner reported two cases in children with thrombosis of the longitudinal sinus, the first complicating otitis, the second following upon a widespread eczema. A pneumococcus in the first case was isolated from the blood-tinged spinal fluid and from the thrombus itself. In the second case a streptococcus was isolated also from slightly blood-tinged spinal fluid and from the removed thrombus. In both cases there were no signs of meningeal involvement demonstrable at autopsy. Voss also observed on three occasions the presence of organisms in the spinal fluid without the slightest sign of meningeal involvement, twice with sinus thrombosis, and once with sepsis of otogenic origin without thrombosis. Voss states that in one-fourth of his cases of sinus thrombosis, bacteria were present in the spinal fluid without complicating meningitis being evident. In two cases organisms were present in the spinal fluid when no sinus thrombosis was present, yet with no meningitis at autopsy.

Are these instances of very early cases which would have developed meningitis had they lived longer? There are those who favor this hypothesis

(Pfaundler and Gerhardt), the latter of whom quotes a similar expression of opinion by Lesnee. Others believe (Voss) that the presence of organisms in the spinal fluid is not always indicative of early or threatened meningitis, but may be found when organisms are present in the blood stream—a sort of seepage by way of the choroid plexus. According to the latter author, the virulence of the organism is an important factor and may be lessened by such passage from the blood stream.

To us such a discussion appears to have only academic interest. It cannot alter the fact that a turbid spinal fluid which contains pyogenic organisms determines the presence of a purulent meningitis. It is perhaps possible that non-active but living organisms may be demonstrable in a clear spinal fluid and yet no meningitis be present, but when the cerebro-spinal fluid is turbid and not contaminated by blood and contains organisms, then a true meningitis must be diagnosed.

#### LOCALIZED VERSUS DIFFUSE SUPPURATIVE MENINGITIS

Writers have long pondered over this subject of localized and diffuse purulent meningitis, some contending that only in localized cases is recovery possible. The German literature particularly often goes into a long discussion of the problem. That we are on controversial ground in a question of this nature is not to be disputed. There is no way of differentiating clinically between the two types, although some authors have attempted to do so by comparison of the severity of symptoms. We do not believe that this can be done with sufficient accuracy to ar-

rive at any clinically helpful or trustworthy conclusions drawn from such observations.

Whiting, from a large experience, says "I have always said, namely, that our cases of general suppurative meningitis all die." Alexander, on the other hand, stresses the impossibility of clinically differentiating diffuse from localized meningitis and believes that his case of recovery was one of a diffuse purulent type. Only ultimate autopsy in recovered cases might help solve this problem. Day's case, which came to necropsy two years after a streptococcus meningitis, showed what appeared to be only a localized area of adhesions cementing down the membrane and obliterating a limited area of arachnoid space. That these findings prove beyond possible doubt the localized nature of the meningitis, we do not believe to be true. It is possible that the drainage strands may have caused sufficient traumatic inflammation to produce adhesions in the area thus injured.

#### SUMMARY

There is as yet no specific therapy for streptococcus meningitis. With the development of antistreptococcus serum in recent years, however, the rational procedure would appear to be the use of this serum intraspinally, coupled with the effort to eliminate any demonstrable source of infection, particularly of otitic origin. Of interest will be a further study of the value of irrigating the spinal canal with dyes, such as neutral acriflavine, in conjunction with other indicated treatment. The possible value of such a procedure is suggested by our own case and



by the experimental work of Kolmer and his coworkers The possibility of spontaneous recovery from this disease must be kept in mind in attempting to evaluate any therapeutic measures

CONCLUSIONS

1 A case of streptococcus hemolyti-

cus meningitis with recovery is reported

2 Forty additional cases of meningitis due to the streptococcus have been collected from the literature and analyzed The method of treatment upon which recovery followed is indicated in each case

ANALYSIS OF REPORTED CASES

AUTHOR	SEX	AGE	TREATMENT	ORGANISM	REMARKS
Schenke and Streit 1901	M	35	Mastoidectomy	Streptococcus (Type not specified) Only one organism seen on smear	A 35 year old machinist with an ear discharge since November 1899 was admitted April 27th, 1900 complaining of severe headache, dizziness and vomiting There was tenderness over the left mastoid and along the spine and pain on moving the head There was a discharge from the left ear Temperature moderate He was operated on April 28th and mastoidectomy revealed sclerosis of the bone and pus in the mastoid cells The antrum mucosa was of dirty greenish color The spinal fluid was slightly cloudy, the smear of which showed no collection of leucocytes but in one preparation a single short chain streptococcus was seen The culture of this fluid was unfortunately not further studied On three other occasions the culture of the spinal fluid was sterile The patient was discharged May 12th, still having some left hemicrania and a discharging ear In November 1900 he was well except that strenuous work produced headache In July 1901 there was a return of discharge from the left ear
Walter Schulze 1903	M	12	Lumbar Puncture	Streptococcus (Type not specified)	Patient a boy aged 12 admitted September 3 1902 History of suppurative otitis in early childhood which never gave trouble again until July 1902 Ear discharged from July until he came to hospital Rather drowsy on admission, vomited at times, hyperaesthetic pain on pressure over cervical spine, marked tenderness behind right ear Developed left facial paresis, continued to vomit Temperature up to 102 F September 4th Patient stuporous herpes labialis is present Lumbar puncture—fluid cloudy under increased pressure about 25

AUTHOR	AGE	SEX	TREATMENT	ORGANISM	REMARKS
					<p>cc removed Leucocytes present On a smear stained 40 minutes a short chain streptococcus and a few diplococci were seen, "which were apparently also streptococci" Still complained of headache, marked stiffness of neck Pupils unequal</p> <p>Until September 16th Ran an irregular temperature but seemed somewhat improved, then developed edema and tenderness behind right ear Lumbar puncture water clear but without bacteria</p> <p>Operation revealed subperiosteal abscess, large deeper abscess was also opened, the sigmoid and transverse sinus were exposed The former was yellowish white in its upper portion, between the sinus and the overhanging bone the dura was loosened anteriorly and above, the extradural abscess extended into the middle cranial fossa No blood flowed from the incised sinus A grayish black thrombus was present September 19th, improved Purulent discharge continued from ear Temperature normal</p> <p>September 28th Wound granulating</p> <p>October 3rd Ear dry and on October 13 wound healed and patient discharged It will be noted that the spinal fluid prior to operation had become clear and the author notes his belief that healing of the meningitis had already occurred before the procedure of operation was undertaken</p>
Voss 1905	7	F	Mastoidectomy	Streptococcus (Type not specified)	<p>The data in this case is meagre Patient was a blind girl aged 7 in whom recovery followed otitic meningitis The condition occurred as a complication of scarlet fever and mastoiditis Mastoidectomy was done The spinal fluid was blood tinged and stood four hours before it was smeared and stained The smear showed gram positive diplococci and short chained streptococci A few lymphocytes were present</p>
Alexander, G 1908	10	M	Operative incision of semi circular canals opening of vestibule and cochlea Incision of the dura Lumbar puncture	Streptococcus in spinal fluid (Type not specified) and B coli from the abscess	<p>Chronic suppurative otitis media left Purulent labyrinthitis with fistula Extra dural abscess Suppurative pachymeningitis Discharging right ear for four years In December 1906 operative procedure was done at home with little relief July 19, 1907 operation through old wound as described in</p>

AUTHOR	SEX	AGE	TREATMENT	ORGANISM	REMARKS
					treatment Cholesteatoma found Post operative course of moderate severity Troublesome nystagmus, discharged, however, on July 25 improved and with good equilibration
Alexander, G 1908	24	M	Radical Mastoidectomy	Streptococcus (Type not specified)	Since childhood patient suffered from discharging ear Treated for cardiac condition for past seven weeks Has again been troubled with ears and has headache, occasional dizzy spells and periods of blackness before his eyes accompanied by vomiting Stiff neck present Left ear discharging foul pus Right drum slightly altered October 21st, 1907 Operation done, cholesteatoma found Posterior and middle fossa exposed as well as the sinus Dura incised with the liberation of cloudy cerebro spinal fluid Lumbar puncture gave cloudy spinal fluid Gram positive cocci in diplo and strep formation found October 30th Temperature normal November 23rd Completely recovered
Nutter, A 1929	7	F	Lumbar puncture only	Streptococcus (Type not specified)	Meningitis complicating double otitis media after measles Two punctures were done July 23—July 27, 1929 Recovery complete
Maguid, H 1910	13	M	Radical Mastoidectomy	Streptococcus pyogenes	Boy 13 years old with a history of right sided purulent discharge since age of 10, following scarlet fever 4 days prior to admission severe pain in right ear Doctor removed polyp from right ear This was soon followed by dizziness and vomiting On examination an exostosis was present deep in the right ear canal and the remnant of a removed polyp visible No drainage Slight Kernig sign No stiff neck Spinal fluid cloudy under greatly increased pressure, containing polymorphonuclears and a few gram positive diplococci very much like streptococci Unquestionable streptococci were later cultured from the pus of the perisinus abscess These cultured as streptococcus pyogenes on agar Day after admission radical mastoidectomy right side The mastoid process was filled with dark granulating masses of foul pus an abscess was found with a fresh

AUTHOR	AGE	SEX	TREATMENT	ORGANISM	REMARKS
					thrombus in the lower portion of the sigmoid sinus, the lateral wall of which was resected. Dura was normal. After the operation pain on bending head, and a positive Kernig sign were present for a time. After 14 days patient up and about.
Graef, C and Wyn- koop, R B 1910	24	F	Autogenous Streptococcus vaccine	Streptococcus (Type not speci- fied)	March 20, 1910. Submucous resection of nasal septum under cocaine anaesthesia. Vomited several times next day. On 2nd day post-operative developed headache with sudden rise in temperature to 104° F. Pain in spine and nape of neck. Marked convergent strabismus and delirium on following day. On March 27th, cloudy fluid obtained on spinal puncture, culturally sterile but on smear gram negative cocci arranged in pairs. March 30th a second spinal puncture gave cloudy fluid which showed streptococci on culture. Patient in low muttering delirium. April 2nd was given autogenous vaccine 10 million organisms and a similar dose daily for five days. The dosage was then increased 3 million a day until 25 million was reached. This level was kept for five days and the vaccine then given twice a week.  The patient was discharged cured 38 days after admission to hospital.
Ohnacker, Paul 1911	5	F	Mastoidectomy Anti strepto- coccus serum intraspinaly	Streptococcus (Type not speci- fied)	Girl age 5—admitted February 15 with severe scarlet fever. Temperature subsided in few days. February 21st and 25th redness was noted, drum ruptured spontaneously and temperature subsided. February 27th—Temperature again elevated, drum incised, no relief. Stiff neck and Kernig present. Mastoidectomy was done and pus found in antrum. The lateral sinus was involved and hence freely exposed. Puncture liberated a chocolate colored fluid mixed with pus particles, the thrombus present was removed till free bleeding occurred. Culture of granulations found at operation gave a long chain streptococcus. Lumbar puncture next day gave a clear sterile fluid. After a week the temperature and symptoms subsided only to rise again. March 10th Left ear drum now involved and mastoidectomy done. After a few days of improvement, again symp-

AUTHOR	AGE	SEX	TREATMENT	ORGANISM	REMARKS
					<p>toms of meningitis Repeated lumbar puncture, though sterile, contained numerous leucocytes Two injections of 20 cc of antistreptococcus serum were given intraspinally</p> <p>Radical mastoidectomy was done Through a defect in the dura from which spinal fluid oozed in large amounts, a puncture was made, yielding cloudy serous fluid mixed with blood from which streptococci were cultured After several sequestra were discharged, healing occurred, recovery took place and patient was up June 15th</p>
Tedesco, Fritz 1911	20	F	Repeated Lumbar Puncture	Streptococcus (Type not specified)	<p>Sudden onset with headache, vomiting, fever April 12, 1911 Bluish spots on body developed but these disappeared in two days</p> <p>Admitted 4/16/11—with stiffness of neck and bilateral Kernig, optic neuritis present 25 cc of cloudy fluid under increased pressure removed, temperature 102.5 4/19/11 lumbar puncture repeated and again on 4/28/11 Made gradual recovery and was up May 9th, 1911</p>
Day, F. W.	Not given	Not given	Dural Drainage Twisted strands of cat gut inserted be- tween dura and brain tissue	Streptococcus (Type not specified)	<p>Four days after evacuation of temporosphenoidal abscess, symptoms of meningitis with turbid spinal fluid Convalescence uneventful Discharged after several weeks Re-admitted two years later with recurrence of abscess in the old cavity, and died from rupture of an undrained pus pocket into the lateral ventricle</p> <p>Note One half hour after death a canula was introduced into the posterior horn of the lateral ventricle and an exit given by a needle in the lumbar spinal canal A methylene blue solution introduced above appeared in fast drops at the lumbar needle At autopsy the subdural arachnoid was stained blue, except for an elliptical area four inches by two inches on the outer and under surface of the temporal and cerebellar lobes of the left side into which the staining solution had not penetrated The membranes were here cemented together and the arachnoid spaces destroyed This clear area corresponded to the center of the region in which the dural drains were used two years before The writer suggests the possibility that in re-</p>

AUTHOR	AGE SEX	TREATMENT	ORGANISM	REMARKS
				covered cases the lesion is anatomically localized, though clinically giving symptoms of diffuse meningitis
Day, E W 1913	19 F	Anti streptococcus serum intraspinally Autogenous streptococcus vaccine subcutaneously	Streptococcus (Type not specified)	Operated on December 6th, 1908 for a simple mastoiditis 15 days later evidence of diffuse suppurative meningitis After 48 hours 10 cc of anti streptococcus serum intraspinally and 12 hours later 100,000,000 dead streptococcus (autogenous) vaccine was given subcutaneously Both injections were repeated in 48 hours, on the 5th day spinal fluid less turbid Temperature normal on 8th day Several additional subcutaneous vaccine injections were given during convalescence Well when seen 4½ years later
Barth 1914	19 F	Lumbar laminectomy and drainage	Streptococcus (Type not specified)	15 days after an injury to her back incurred Dec 25th developed headache and vomiting, and 5 days later admitted to the hospital Turbid spinal fluid at first showed no organisms On January 29th streptococci were isolated from the spinal fluid January 31st lumbar puncture, laminectomy and drainage (3rd and 4th lumbar) were done After a stormy course gradually improved February 20th the drain was removed Toward end of March patient out of bed and apparently recovered This author believes that streptococcus meningitis is a surgical disease, just as acute peritonitis is surgical
Leighton and Pringle 1915	8 F	Lumbar laminectomy and drainage	Streptococcus (Type not specified)	5 weeks before onset sore throat, 3 weeks before onset otitis media and swelling behind ear Admitted December 16th, 1914 and condition diagnosed as mastoiditis 3 days later typical meningeal symptoms On lumbar puncture bloody fluid obtained Under ether anesthesia December 19th, 1914 lumbar laminectomy (3rd and 4th lumbar) done Post operative course stormy, but improvement progressive Temperature normal January 4th, 1915 Discharged February 6th, 1915
Du Bois P L and Neal, J B 1915	26 M	Antistreptococcus serum intravenously and intraspinally and streptococcus vaccine subcutaneously	Streptococcus pyogenes	Onset 8 days after incised ear drum for otitis media, anti-streptococcus serum was given intraspinally and intravenously and also streptococcus vaccine subcutaneously On the 6th day difficulty in obtaining fluid was encountered and the taps stopped Urotropin

AUTHOR	AGE	SEX	TREATMENT	ORGANISM	REMARKS
			Urotropin up to 120 grains per day		was given from the onset 30 grains per day and then up to 120 grains per day Slight tremulousness and pain in back and extremities developed and except for impaired sensation and weakness, pain cleared with salicylates
Mc-Kenzie, Dan 1915	50	M	Surgical procedure Incision and drainage of spinal fluid through dura	Streptococcus (Type not specified)	Left mastoidectomy in September 1914 October 22, 1914, radical mastoidectomy was done on both sides An eroded bony sequestrum removed on right side, October 25th—Headache, fever, irritability October 28th—stiff neck—20 cc of spinal fluid from which streptococci were cultured Operation—dura on right side incised, liberating free flow of spinal fluid Wire drain in internal auditory meatus No lateral sinus disease Gradually improved Temperature normal November 18th
Leighton and Pringle	65	M	Lumbar laminectomy and drainage	Streptococcus (Type not specified)	Onset three weeks after injury to head which knocked him unconscious for a few minutes Lumbar laminectomy under spinal anesthesia Loss of sphincter control for nine days Regained consciousness after two days Drain removed on 5th day, gradual recovery Slight meningocele developed
Crockett, F A 1916	16	M	Lumbar puncture antistreptococcus serum	Streptococcus (Type not specified)	Double otitis media following measles 4 days later mastoidectomy, bilateral, done, with complete healing in 12 days 3rd day post operative became comatose Questionable stiff neck and double Kernig Temperature 104 Lumbar puncture clear but on centrifugation streptococci found on smear 2 days later convulsions followed by right facial paralysis and weakness on right side of body lasting two days Streptococcus serum given intravenously on 1-2 occasions Urotropin by mouth Made gradual recovery
P. A. 1917	21	M	Radical Mastoidotomy	Streptococcus pyogenes	Admitted October 26, 1915 in semicomatose History difficult to elicit, answers questions when aroused and goes off to sleep again Vomiting and fever for 12 days prior to admission For 6 months ear trouble on right side  Marked stiffness of neck Positive Kernig Temperature 104 F Left ear normal Right ear discharging a fetid pus

AUTHOR	SEX	AGE	TREATMENT	ORGANISM	REMARKS
Bondy 1917	43	M	Labyrinthine Operation	Diplostrepto- cocci	December 27th Mastoid opened and found sclerosed Pus and broken cholesteatoma in mastoid and antrum Radical operation done, dura exposed in the middle fossa and extra dural abscess found The dura was covered by greenish exudate Exposure carried till healthy dura found but medially this was not possible The dura was slit and an iodoform wick placed in the sub dural space Lumbar puncture yielded cloudy fluid under markedly increased pressure, containing streptococcus pyogenes
					October 28th Temperature about 102 Slightly clearer mentally
					October 29th Temperature practically normal but complaining of headache Epileptiform seizure of Jacksonian type at noon
					October 31st Two epileptiform seizures
					November 2nd Spinal fluid clear
					November 3rd Patient again comatose Temperature 100 Marked stiff neck, Kernig and stertorous breathing
					November 10th Gradually improved Lumbar puncture clear and sterile
					November 18th Up a little while
					November 25th Neurological examination negative except for sensitiveness over vertebrae
					January 31st Discharged home
					Admitted April 7, 1915 Since childhood purulent infection and difficulty in hearing—both ears
					April 8th Radical right mastoid-ectomy Mastoid sclerosed, cholesteatoma present
					April 15th Up and about
					May 17th In an attempt to remove polypi, which had formed, by means of a wire snare the wire broke and the instrument was pressed in There was prolonged nystagmus and dizziness but the patient managed to go home alone



AUTHOR	AGE	SEX	TREATMENT	ORGANISM	REMARKS
					<p>May 18th Vomiting and dizziness set in abruptly. He returned to the clinic complaining of vomiting and severe headache. Nystagmus was present toward the healthy side.</p> <p>May 19th Stiff neck, right positive Kernig sign, severe headache. Temperature 102.2 F.</p> <p>Labyrinthine operation, vestibule opened, exposed dura normal. Lumbar puncture showed cloudy fluid containing diplo-streptococci.</p> <p>May 20th Temperature normal though meningeal signs and nystagmus less. Kernig still present.</p> <p>May 31st No nystagmus, meningeal signs have entirely cleared up.</p> <p>July 12th Discharged from the hospital. Wound clean, no complaints except for occasional dizziness.</p>
Bondy 1917	28	M	Lumbar Puncture	Streptococcus pyogenes	<p>Admitted March 27th, 1916 complaining of severe headache for the past ten days. On February 24 was operated on at a military hospital for acute right mastoiditis and wound has been draining since. Operated on April 1st, by incision through old scar, granulations removed, and exploration continued until dura of the middle fossa and the sinus were exposed. Headache persisted after operation and temperature remained elevated.</p> <p>April 21st Severe headache. Unable to sleep at night. Some visionary disturbance. Right 6th nerve weakness, again operated upon, wound cleaned and granulations removed. Probing in several directions yielded nothing. Lumbar puncture slightly turbid but under normal pressure contained streptococci.</p> <p>April 26th Lumbar puncture blood tinged, containing streptococcus pyogenes.</p> <p>May 3th, Lumbar puncture sterile.</p> <p>July 3th. Recovery complete. Wound healed. Temperature subsided in 12 days but abducens paralysis did not clear completely for 8 weeks. Discharged home.</p>

AUTHOR	AGE	SEX	TREATMENT	ORGANISM	REMARKS
Weaver, G H 1919	25	F	Antistreptococcus serum.	Streptococcus viridans	Onset September 23 Temperature normal on October 12 and stayed normal till October 17th, then exacerbation of meningeal symptoms, treatment continued, reached normal October 23rd "The improvement that followed each administration of anti-streptococcus serum was striking"
Watson-Williams 1920	37	M	Silver preparation (collosol argentum) intraspinally	Streptococcus (Type not specified)	Admitted September 23, 1919 with pain in the left ear and dizziness Purulent discharge from left ear since boyhood September 25th Headache, vertigo, spontaneous nystagmus to left September 26th Lumbar puncture turbid Mastoidectomy and labyrinthotomy was done September 28th Lumbar puncture October 2nd Somewhat improved October 6th Severe headache again, lumbar puncture done, 15 cc of cloudy fluid removed and 1 cc of collosol argentum injected Streptococci were cultured from spinal fluid October 7th 3 cc of collosol argentum intravenously Spinal fluid still turbid October 8-10th Daily lumbar puncture preceded by 3-5 cc of collosol argentum intravenously Made a gradual but complete recovery
J B Neal, 1921	5	F	Lumbar Puncture	Streptococcus hemolyticus	Onset following otitis media Slight stiffness of neck, headache, irregular temperature up to 105 Spinal fluid had a practically normal sugar content The author believes this to be a case of localized meningitis No intraspinal injections were given only lumbar puncture being resorted to Recovery ensued
Shaw, Henry 1921	8	M	Lumbar Puncture	Streptococcus hemolyticus	Left ear incised October 24th followed by good drainage Developed headache which continued On November 10th left squint noted November 15th Temperature rose to 104, marked hyperaesthesia was present Spinal puncture gave a clear fluid containing only 18 cells For two days there was slight improvement but on the third day meningeal symptoms were again in evidence and the temperature rose Lumbar puncture now

AUTHOR	AGE	SEX	TREATMENT	ORGANISM	REMARKS
					taneously 2 days 9 days post-operative, temperature normal Recovery uneventful
Dandy 1924	49	M	Surgical drainage by way of cisterna magna	Streptococcus viridans	8 days after removal of cerebello-pontine tumor rise of temperature, drowsiness, irrational Spinal fluid showed streptococcus viridans On 18th day surgical drainage of cisterna magna which continued 4 days Then daily or twice a day punctures of lateral ventricle, spinal canal or of cerebellar cisterna, temperature still elevated 43 days after onset of drainage Recovery ensued
Vining and Thompson 1924	10	F	Antimeningococcus and antistreptococcus serum	Short chain streptococcus markedly hemolytic in character.	Two weeks following an acute tonsillitis which subsided spontaneously, developed meningeal signs, headache, stiff neck, positive Kernig Lumbar puncture yielded 20 cc of cloudy fluid P-60%, L-40% No organisms in direct smear Next day after removal again of 20 cc, 15 cc. of antimeningococcus serum was given intraspinally and 10 cc subcutaneously Polymorphonuclears 64%—lymphocytes 36% Fluid showed short chain streptococcus markedly hemolytic in character Improvement on 2nd day following tap 3rd tap on third day showed less turbidity 10 cc. of antistreptococcus serum injected subcutaneously, 4th day distinct improvement, 5th day 6 cc of clear fluid obtained
Urbant-schitch, E. 1926	21 m's	M	Lumbar puncture Anti-streptococcus serum  Mastoidectomy  Urotropin intravenous	Streptococcus mucosus	Admitted June 6th, 1926 with history of head cold and bronchitis 8 days prior, child had poked a match in its left ear Onset sudden January 4th with vomiting and fever On admission no stiffness of neck, Kernig doubtful, ears normal Lumbar puncture, not under pressure, a bloody tap from which streptococcus mucosus was cultured On January 8th fluid under increased pressure Despite essentially normal drums bilateral mastoidectomy done and pus found January 9th Lumbar puncture 2½cc of antistreptococcus serum given January 10th Three attempts at lumbar puncture unsuccessful January 14th Lumbar puncture under fairly marked pressure slightly cloudy, 3000 cells per cmm., continues to run an irregular course of temperature January 21st Spinal fluid still turbid but

AUTHOR	AGE	SEX	TREATMENT	ORGANISM	REMARKS
					sterile Both ears discharging January 28th Still having evening temperature up to 103 or more Lumbar puncture under greatly increased pressure and containing streptococcus mucosus February 1st Gravely ill, marked stiffness of neck Kernig positive February 2nd 5 cc of 40% urotropin intravenously February 4th Lumbar puncture unsuccessful February 5th Improved and continued to grow better despite occasional rises in temperature Discharged home February 21st Through March and April, draining ears and several bouts of fever Ears ceased draining April 27th He became entirely well July 7th Continues perfectly well
Neal, J B and Jones, A 1927	7	F	Anti scarlatinal serum of anti toxic and anti bacterial potency On one occasion $\frac{3}{4}$ cc of 1% neutral acriflavine was added At onset anti meningococcus serum was used	Hemolytic streptococcus belonging to the "chief scarlet fever group"	Mild scarlet January 20, 1927 lasting two days, following which she was well On the 5th day after onset, fever, headache and meningeal symptoms Admitted on 10th day Left suppurative otitis media present but no indication of mastoid involvement Pyelitis was a complication, improvement began 2/14/27 Discharged 3/13/27 in excellent condition "The high mortality of streptococcus meningitis is shown by the fact that this is only the 3rd case to recover among the 116 that have been seen by the meningitis division"
Huenekens E J Stoesser, A V 1927	7	F	Daily lumbar puncture, irrigation with normal saline	Streptococcus hemolyticus	Onset following 2 days after incision bilateral otitis media Bilateral mastoid operation was immediately done 9th day post operative, improved 16th day exacerbation, after 12 days treatment, recovery Mental condition normal three weeks after
McCarthy, F P 1927	25	M	Daily lumbar puncture Normal human serum intraspinally	Streptococcus viridans	Onset 2 months following severe injury to head, fever, chills and delirium Improved on 8th day following treatment Discharged after 1½ months No sequela or complaints Slight spasticity of legs at first, later cleared entirely
Lang 1928	2	M	Antimeningococcus serum Scarlatinal antitoxin intraspinously and intravenously (seven doses)	Streptococcus hemolyticus	A boy, aged 2, was admitted to the Babies hospital with a negative family history, he had never been sick before He had been nursed for seven months The present illness began abruptly five weeks before admission, with fever 104.5 F and sore throat, which persisted A diagnosis of scarlet fever without

AUTHOR	AGE SEX	TREATMENT	ORGANISM	REMARKS
Neal J. 1928 1929	11 M	Continued anti- bacterial and antitoxic serum (scarlet) intra- -ly, all, and in- traventricularly. Spinal punc- ture in dis- tortus puncture.	Hemolytic Streptococcus	<p>a rash was made, and antitoxin was given. The child was sent to a hospital for contagion, where he stayed two days and was then sent home as "no case." Restlessness, constant crying, refusal of food and loss of weight were prominent symptoms during the first five weeks of illness. Two lumbar punctures and a blood culture gave negative results. Both ears were incised and discharged freely.</p> <p>Physical examination showed a well developed white, male child acutely ill, with a temperature of 102 F, and extreme irritability. The fontanel was closed and the neck rigid, right internal strabismus and Tache were present, and the Kernig and Brudzinski signs were positive.</p> <p>Lumbar puncture on admission showed cloudy fluid with 1,000 cells, 99% of which were polymorphonuclears. Globulin was present and sugar absent. Gram-positive cocci in chains were found in spreads made from the fluid, and cultures grew streptococcus hemolyticus.</p> <p>The urine showed a small amount of albumin, but was otherwise normal. Antimeningococcus serum was given at the onset, with a resulting rise in cell count. Scarlatinal antitoxin was then given intraspinaly and intravenously (seven doses), causing a gradual rise at first in the spinal fluid cell count which then gradually diminished to 2,500. The spinal fluid sugar remained below 20 mg. The child was given two blood transfusions, and the spinal fluid cultures were positive for streptococcus hemolyticus on three different occasions.</p> <p>At present at the age of 4, he is well grown and well nourished, but mentally sub-normal. He still has attacks of irritability.</p> <p>Patient 11 years old, had an attack of scarlet fever on April 2nd, 1928. Two weeks later there was otitis media of the right ear. He began having meningeal symptoms on April 27th and was admitted on May 1st. He presented typical signs of meningitis, there was an internal strabismus of the left eye and double otitis media. The blood count was 5,900, polymorphonu-</p>

AUTHOR	AGE	SEX	TREATMENT	ORGANISM	REMARKS
					clears 85%, Lymphocytes 15% The blood culture was negative and the urine was normal He received the combined anti-bacterial and anti-toxic serum (scarlet) prepared under the direction of the New York Board of Health, intraspinally on the third, fourth and fifth of May He also received 5000 units intramuscularly on May 3rd Two of the spinal fluids showed a hemolytic streptococcus which was also obtained from a cisterna puncture performed on May 18th, on which occasion no serum was given He made a complete recovery and reported 1½ years later apparently well
AUTHOR	AGE	SEX	TREATMENT	ORGANISM	REMARKS
Rosenberg and Nottley 1931	6	F	Lumbar puncture Anti meningococcus and anti streptococcus serum and 1-4000 aqueous solution of neutral acriflavine intraspinally	Streptococcus hemolyticus	Admitted February 23, 1929 with a history of acute tonsillitis six weeks previously This was soon followed by backache, headache and vomiting There was stiffness of neck, irritability and restlessness Ears normal Spinal tap gave turbid fluid under increased pressure Prior to isolation of streptococcus anti meningococcus serum was given, then antistreptococcus serum Failing to improve on this therapy neutral acriflavine 1-4000 aqueous solution was used to irrigate the spinal canal Improvement was gradual but progressive and the child made a complete recovery

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# The Prognosis in Tuberculosis with Especial Reference to the Psychological Aspects

By E. W. HAYES, M. D., Med. Dir. Dore Sanatorium, *Monrovia, California*

**M**Y PURPOSE, for the most part, in this discussion is to present some of the phases which have to do with the prognosis of pulmonary tuberculosis that come directly under the control of the physician and which I feel, in the majority of cases, determine the outcome.

It seems to me that, particularly in the past, as we have come in contact with pulmonary tuberculosis we have had a tendency to base our opinion regarding the prognosis largely upon the extent of the involvement or upon the feelings and appearance of the patient or perhaps more or less upon both of these taken together. Experience, however, has taught us that feelings and appearance are extremely deceptive and that, while the prognosis in general is better in the less extensive than in the more extensive cases, yet a certain percent of the early cases go on to a fatal termination while a certain less percent of the more advanced cases recover. Consequently, we have now come to realize that we must get away from giving an arbitrary opinion in any case and that we must regard the prognosis as rather an individual affair and that the outcome can be determined only as we follow the case along.

However, about the first thing those of us who are handling tuberculosis patients are called upon to do is to give

an opinion as to the outcome, and this demand is repeated from time to time during the course of the disease. In order, then, to satisfy not only our own minds to a certain extent, but particularly to satisfy our patient and, in many cases, his relatives, we must formulate some idea about the prognosis.

Having had an opportunity to carefully study and observe a case over a period of a month or more, it is possible perhaps to have some idea of the outcome through a proper evaluation of the important symptoms and, to a less extent, by the evaluation of the indication of the physical signs. As Lawrason Brown has said, it is the symptoms which tell us what is going on at any particular time. Consequently, as, in a general way, the symptoms increase or decrease, the prognosis is unfavorable or favorable. Dr. Brown says also that the physical signs tell us what has taken place in the past. But periodic physical and x-ray examinations, as they may indicate an increase or decrease in the physical signs and the extent of the involvement, will give us some definite information as to the progression or retrogression of the disease. In forming these general ideas about the outcome we should bear in mind that the course of the disease may change from month to month and with



it the symptoms and physical signs, so that our opinion regarding the prognosis may change accordingly.

We should also remember that since there are so many different factors which influence the course that a case of pulmonary tuberculosis pursues and since so many of these factors are dependent upon the individual element, we never see two people who have tuberculosis alike any more than we see two people who look alike, act alike, or talk alike. Dogmatism, then, in the prognosis of tuberculosis is not possible.

In general we should keep in mind that today tuberculosis is regarded as the most curable of chronic diseases, that active pulmonary tuberculosis, regardless of the extent, is always serious, at least until the physician and the patient regard it seriously. Again, we should remember that pulmonary tuberculosis is cured by attention to details, that a certain few patients with pulmonary tuberculosis, although they disregard details, get well in spite of what they do rather than because of what they do, but that for everyone who gets well under these conditions perhaps from forty to fifty people that ought to get well under proper circumstances lose their lives because, through their own neglect or through outside influence or advice, they have disregarded the details of the cure. We hear little of the story of these people who die, however, because dead men tell no tales.

As I have said, the prognosis in tuberculosis is, at best, uncertain because it depends upon so many different factors, such as age, sex, habits, and opportunity to take the cure, which are more or less fixed while others, such

as the virulency of the infecting bacilli and the resistance of the one infected not only differ in each case of pulmonary tuberculosis, but are changeable and are greatly modified by the way in which the patient adjusts himself to the cure and by the way he reacts to the cure.

In other words, at the beginning of each case of pulmonary tuberculosis we can conceive of a certain virulency of the infecting bacilli and a certain resistance of the host. The ultimate outcome of the contest waged between these two antagonists is what determines whether the patient lives or dies. The contest, however, during the course of the disease, is influenced by many factors which tend to increase or decrease the resistance of the host and at the same time decrease or increase the power of the bacilli to grow and produce destruction. The factors which have the greatest bearing upon the outcome of this contest in most cases are the psychological reactions of the patient while he is endeavoring to take the cure, and it is to these that I want particularly to call your attention. Today it is generally conceded that from eighty to ninety percent of the influences which determine the prognosis are psychological and have to do with the emotional, mental and nervous reactions of the patient.

I have referred in a general way to some of the factors which influence the prognosis in tuberculosis over which the physician has little, if any, direct control. It is true that in a certain small percentage of the cases of pulmonary tuberculosis such factors may control the situation and determine the outcome. However, in the vast majority of cases the outcome is not de-

terminated by these more or less fixed factors, but by the more important variable or changeable factors which change or vary according to the psychology of the patient. It is these changeable factors which may and should come under the immediate control of the physician. And this is where we as physicians, entrusted with the responsibility of guiding patients with pulmonary tuberculosis back to health, find our opportunity, for the most part, to discharge that responsibility.

While the diagnosis of early tuberculosis is not an easy matter, yet, the diagnosis having once been made, the most serious task and responsibility of the physician remains. In every branch of medicine the physician must assume full responsibility for his patient. In tuberculosis this responsibility is not only great, but it is strenuous because of the nature of the disease and the nature of the cure with its long drawn out course. We should regard a patient with active pulmonary tuberculosis with the same seriousness with which we would regard a patient with acute appendicitis. The issue is the same in each case, that is, the outcome is uncertain and the life of the patient is at stake.

We cure tuberculosis by raising the resistance of the body against the inroads of the tubercle bacillus. The most important factor in raising this resistance is rest, and by rest we mean not only physical, but emotional and mental relaxation.

Generally speaking, the treatment of tuberculosis involves a mapping out of a mode of life with attention to details. The skill of the physician in determining the mode of life necessary for any particular case and his skill in

influencing the patient to abide by that mode of life with an optimism and enthusiastic regularity measures his ability to influence favorably the prognosis of tuberculosis.

It is true that certain patients are so constituted temperamentally that, once the nature of the cure and the importance of its various phases are explained to them, they are able to follow it cheerfully and more or less rigidly. This, however, is not true of the average patient. To expect the average patient, who is accustomed to the duties and responsibilities of ordinary life, to suddenly give up his usual ways of doing and living and thinking and cure his tuberculosis after he has been simply advised that he needs a rest or that he must take life easy, is as impractical as it is to expect a ship that has been turned loose on the seas without a pilot to reach a given port.

Again, in pulmonary tuberculosis the nature of the disease is such that its poisons seem to affect the centers of nervous and mental control of those afflicted so that these centers are in a state of unstable equilibrium. We must realize, then, that we are not dealing with normal individuals, but with people who, for the most part, are not only physically, but mentally and nervously sick. In other words, if we as physicians are to do our duty in aiding these patients to recover their health, we must study them and understand them and supervise them so that we can control them mentally and emotionally. As we all know, the emotions have a very direct effect upon the functions of the body. Crile has said, "Emotions drive the organism with extreme intensity and may cause exhaustion or shock." He further adds

that at autopsy certain definite changes in tissues such as the brain, liver and other organs are found which are due entirely to the emotions. Likewise we are not able to control these patients physically until we first have them under control mentally and emotionally.

Many patients fail to make the proper effort to take the cure because they either have not been made to understand the seriousness of their condition or because they have not been made to understand what taking the cure means. Again, many patients who are extremely refractory when first told they have tuberculosis and what they must do to get well, often, in a relatively short period, prove to be excellent patients provided they are made to understand the situation as they should.

Many of the disturbing influences which interfere with the patient's progress once he is started on the cure, are the result of a state of mind. For example, patients who state that it is impossible for them to adjust themselves to the details of the cure because they are so nervous and who cannot eat or sleep and have an unproductive, racking cough, usually, after they have been reassured that these symptoms are not a serious indication, but are largely the result of a state of mind and that they have it within their own power to overcome them, are, for the most part, relieved of these conditions in a very short time. Those who deal with tuberculous patients not only continually witness such adjustments to the cure which come as the result of reassurance based upon a proper understanding of the facts, but they also see the marked improvement in the general condition of the patient, which results

The physician, then, who deals with tuberculosis, must understand not only tuberculosis and its peculiarities, but he must also understand human nature and its various peculiarities, because it is on his ability not only to properly understand and control his patient, but to buoy him up and inspire him to cheerfully continue for perhaps months or even years what would otherwise seem a monotonous and hopeless task that a favorable prognosis often rests.

Our control of the patient's mental and emotional state is secured by our attitude toward the patient, by our ability to impress him with our understanding of his disease and of his feelings and with our personal interest in his case, and finally by our ability to assist the patient in taking the cure in an environment wherein he is assisted in his physical, mental and emotional efforts to the utmost.

Our first step from a psychological consideration, which makes for a favorable prognosis, is to truthfully explain to the patient the extent of his disease as well as the nature and the purpose of the cure. The nature of the cure is such that unless patients understand their condition thoroughly and what they must do to recover their health, they cannot follow it as they should. It is the uncertainties in life, whether they have to do with health or other serious matters, that cause worry, restlessness, and emotional disturbance, and a simple, but frank explanation of the facts goes a long way toward establishing that bond of confidence which should exist between patient and physician. At the same time, there are very few patients who cannot face the truth if it is put up to them optimistically. The patient and his rela-

tives must be made to understand that the patient is the one who must take the cure and that the physician's duty is to aid him by advice and intelligent guidance

In administering this advice and guidance, the physician must so place the patient that he will be aided by his environment. We are all more or less the products of environment and this is particularly true of patients with tuberculosis because of the nature of the life they must lead and because of the unstable condition of their centers of control. Consequently, tuberculous patients are better able to carry out the necessary details which make for a favorable prognosis when they are so placed that they have the moral support and mutual sympathy of those around them and when they are under the continuous care and supervision of those who understand and appreciate their mental and nervous disturbances. Experience has proven that patients who take the cure surrounded by those who do not appreciate the nature of tuberculosis and the particular effect it has upon the patient and the importance of a detailed, enthusiastic mental cooperation on the part of the patient, in general have a less favorable prognosis. Their efforts at taking the cure are very often haphazard and too often they give up even those efforts before their condition warrants anything like a favorable prognosis. That is, they do not stay on the cure long enough and, while some of them under these circumstances may be able to get by for months or a few years, they eventually break again because they have not given themselves time enough to get a permanent arrestment.

In tuberculosis there is no factor

more important in the prognosis than time. Many patients who would otherwise recover lose their lives because they do not stick to the cure long enough. With few exceptions, patients who give up the cure too soon do so because we have not instilled into them the right prospectus of tuberculosis and the essentials for its cure. That is, we have failed to influence their train of mind so as to hold them on the cure.

The length of time that it is necessary for any patient to stay on the cure is an individual matter. It must be sufficient, however, to give that patient an opportunity to demonstrate that he can or that he cannot overcome his disease. The physician must make the decision as to how long that time should be. This decision should be made not upon the feelings and appearance of the patient, but upon a thorough understanding of the patient in general and particularly upon a proper knowledge of the underlying pathology.

In conclusion, I think we should remember that while we regard tuberculosis as one of the most curable of chronic diseases, that the prognosis in the average case of active pulmonary tuberculosis is, at any given time, uncertain. It is uncertain because it is dependent on so many different factors. The more important of these factors which determine the prognosis vary with the psychology of the individual patient. This psychology depends, for the most part, upon the physician. Consequently, our ability to properly advise, to intelligently guide and to efficiently manage our patient is the outstanding influence in bringing about a favorable outcome in pulmonary tuberculosis.

# Digestive Diseases and the Teeth

By WILLIAM LINTZ, M D , *Brooklyn, N Y*

**I**N A personal communication, Dr. C H Mayo makes a statement that "75% of human ailments come from what goes into the mouth including food and drink, and the diseases of the mouth which cause local and general disease, and focal infections which may remain a cause of disease over a long period of time" From this statement it is at once apparent how important is a study of the teeth in disease in general and in digestive diseases in particular

infected teeth for this was principally responsible for their loss, either spontaneously or by extraction As a rule it was found where a patient had many teeth missing that the remaining ones were in bad shape and conversely where few were missing the remaining ones were in much better condition This is explained by the fact that as a rule people hate to part with all their teeth and dislike wholesale extraction even when indicated, also by the fact that the malocclusion resulting from the loss of a great many teeth leads to deterioration and infection of the remaining ones

Very few patients in this series were ultimately labeled with only a single diagnosis The majority had more than one The missing teeth are classified under each one of the diseases This does not in any way invalidate our statistics, as this was accounted in the ultimate conclusion The digestive disease was the predominating one in every one of the cases of this series

When in a certain disease, the great majority of patients have a high percentage of missing teeth and the remaining ones in poor condition, inference may be drawn that there is an etiological relationship between the infected teeth and the disease To point out this etiological relationship as well as its limitations as gathered from



TABLE II—MISSING TEETH IN NORMAL PERSONS

Age	10-14	15-19	20-24	25-29	30-34	35-39	40-44	45-49	50-54	55-59	60-64	65-69
No. of cases	15	9	15	17	12	10	10	5	3	1	2	1
Total Missing	4	3	3	2	5	10	5	2		2	2	2
Upper Jaw	2	2	2	2	1	10	7	2		2	2	2
Molar	1	1	1	1	7	8	6	3		2	2	2
Bicuspid	1	1	1	1	11	19	13	6	3	4	1	4
Canine	1	1	1	1	25	38	24	15	7	6	2	6
Lower Jaw												
Molar												
Bicuspid												
Canine												
Total Missing	0	8	33	17	91	152	117	46	18	19	10	32
Average per person	6	9	22	10	76	152	117	92	60	19	5	32
Per Cent Missing Teeth												
Males				48				242				158%
Females				52				310				187%
Both sexes				100				552				172%

Total Number of Missing Teeth in Sequence

Upper Jaw	Lower Jaw	Both Jaws
Molar	Molar	Molar
Bicuspid	Bicuspid	Bicuspid
Lateral Incisor	Lateral Incisor	Lateral Incisor
Central Incisor	Central Incisor	Central Incisor
Canine	Canine	Canine
Total	Total	Total
308	244	552

The average loss was 5.5 teeth per patient  
The average rate of loss was 17.2% per patient  
There were 25.2% more upper teeth lost than lower

actual detailed experience obtained from the patient, but which is greatly underestimated and under utilized, or conversely abused by the profession in the treatment of digestive diseases, this paper is written

### CIRRHOSIS OF LIVER

There were six patients in this group, each one had lost on the average 21 or 65% of the teeth. This is rather high. At first glance it seems to be contrary to medical experience to associate cirrhosis of the liver with focal infection. But if one bears in mind the universally admitted relationship between dental infection and the gall-bladder and biliary duct pathology and that these in turn are frequently a factor in cirrhosis of the liver<sup>1</sup>, this apparent incongruity becomes understandable. Another factor enters here which makes these figures so high. I believe that this is one of the diseases where needless extractions are performed on account of the difficulty of establishing the diagnosis<sup>2</sup> and the unsatisfactory therapeutic results. When either one or both of these factors exist, I find that not a few doctors will resort to needless teeth extraction, with the hope of influencing favorably certain existing symptoms. It is therefore advisable to bear in mind the diagnosis of hepatic cirrhosis in cases of dubious pathological indications for dental extraction, which leads to negative results for the relief of symptoms of indigestion. As this is a disease of later life the age factor must also be considered (See Table III). I have no experience with the eradication of focal dental infection in this disease but in the future, I believe in view of the high

percentage of missing teeth it would be worth our while to pay more attention to the teeth in this disease.

### CANCER OF STOMACH

There were seven patients in this group, each patient had lost on the average 62½ percent of his teeth. I do not believe that this implies an etiological relationship. The reason for the wholesale extraction is chiefly in mistaken diagnosis particularly at the beginning of the disease. The teeth are removed because these patients are diagnosed frequently as ulcer of the stomach, chronic cholecystitis, appendicitis, etc., in other words, those diseases in which we have a right to expect good results from the eradication of focal infection (see below). It behooves us therefore in the above mentioned diseases when wholesale dental extraction leads to unfavorable results to retrace our steps that have led to such a diagnosis and to double our vigilance for gastric carcinoma. Age is also a factor in this disease (See Table III).

### PEPTIC ULCER

Over 40 percent of the teeth were missing on the average in each of the twenty-six cases comprising this group. The remaining teeth as a rule were in bad shape. While very few clinicians of experience doubt the close relationship of infected teeth to peptic ulcer, the great majority of surgeons are exceedingly skeptical about this point and pay very little attention to it. Yet this factor is of vital importance for obtaining results in this disease both along medical and surgical lines. Remove the focal infection and the ulcer shows



TABLE III.—Missing Teeth in Disease

	Upper Jaw					Lower Jaw					Average
	Central Incisor	Lateral Incisor	Canine	Bicuspid	Molar	Central Incisor	Lateral Incisor	Canine	Bicuspid	Molar	Total
10-14 yrs	11	..	..	..	4	1	1	..	1	5	7
15-19 yrs	9	..	..	..	7	..	..	..	2	2	10
20-24 yrs	20	..	..	4	20	..	..	..	2	13	31
25-29 yrs	32	7	4	18	29	2	2	2	16	35	112
30-34 yrs	31	3	2	11	29	2	1	2	3	29	86
35-39 yrs	51	16	17	41	91	2	2	5	36	110	330
40-44 yrs	12	12	13	53	92	2	4	6	35	120	352
45-49 yrs	31	27	26	27	98	7	8	9	35	97	401
50-54 yrs	32	27	26	58	96	16	16	15	48	108	435
55-59 yrs	30	35	34	80	130	22	22	21	59	100	548
60-64 yrs	22	23	22	52	83	18	11	8	38	84	360
65-69 yrs	21	38	35	72	109	34	32	34	75	113	580
70-74 yrs	8	11	12	21	39	15	15	11	25	45	207
75-79 yrs	1	2	7	15	22	8	8	8	16	23	123
80-84 yrs	1	2	2	4	6	2	2	2	4	6	32
85 yrs	1	2	2	4	6	2	2	2	4	6	32
Total Cases, 310											

Upper Jaw					Lower Jaw					Totals	
Total Number of Missing Teeth in Sequence					Total Number of Missing Teeth in Sequence					Totals	
Upper Jaw					Lower Jaw					Totals	
Molar	..	..	..	832	Molar	..	..	..	996	Both Jaws Molar	1,678
Bicuspid	..	..	..	500	Bicuspid	..	..	..	399	Bicuspid	899
Lateral Incisor	..	..	..	215	Lateral Incisor	..	..	..	138	Central Incisor	347
Central Incisor	..	..	..	209	Central Incisor	..	..	..	126	Lateral Incisor	341
Canine	..	..	..	202	Canine	..	..	..	123	Canine	325
Totals ... ..	..	..	..	1,958	Totals	..	..	..	1,682	Totals	3,640

The average loss of teeth was 10.4 per patient  
The average rate of loss was 32% per patient  
The rate of loss was 16.4% more in the upper jaw than in the lower.

great tendency to heal. This is true not only in cases of recent origin, but in old chronic cases of long standing as well. Any treatment no matter how thorough is less than half completed unless it includes the eradication of any present focal dental infection. Very often all symptoms completely and permanently disappear when this is performed without any other treatment. This, of course, does not necessarily mean that the teeth are always responsible. The infection may be in the tonsils, sinuses, or any other part of the body. This holds good not only in this disease but in any other disease. But in view of our dental statistics of members of this group which we interpret as exhibiting a high degree of infection both in the past and in the present, backed by therapeutic experience and the results obtained in a large number of cases, I believe that the infected teeth in particular play the most important rôle in this relationship.

Every diagnosis of peptic ulcer must be accompanied by a roentgenogram of the teeth, and that irrespective of their apparent condition. For only too often one finds an abscessed tooth or granuloma in what appears to be a perfect set of teeth. This is usually more than sufficient to cause and account for the ulcer. I find that delay in therapeutic results and recurrences are due to infection which has not been completely eradicated. Autogenous vaccine administration in sufficient dosage to produce moderate local and general reaction, irrespective of the number of bacteria injected, I find an important adjuvant in this treatment.

The following typical case beautifully illustrates some of the enumerated points.

E. K., male, 41 years old, lost 35 lbs in weight, had been suffering periodically for two years with indigestion, occasional vomiting spells and very severe epigastric pain which sometimes penetrated to the back, and very often awakened him from sleep. On physical examination with the exception of epigastric tenderness he was essentially negative. The routine blood and the Wasserman were negative. The blood sugar was 0.18%. A marked glycosuria, acetone, diacetic acid and B-oxybutyric acid were found. The gastric chemistry, feces examination, fluoroscopy and X-ray of the entire gastrointestinal tract were typical of a duodenal ulcer. Cholecystography was negative. Multiple abscessed teeth were discovered on roentgenologic examination. Upon the eradication of all dental infection before any other treatment was instituted all symptoms promptly vanished. Under the proper dietetic regime, medication, insulin and the proper administration of autogenous vaccines permanent relief of all symptoms has been established.

*Comment.* A diabetic, suffering from a large duodenal ulcer of two years standing promptly experienced relief of all symptoms upon the extraction of infected teeth. This resulted in a permanent cure when the usual treatment for this condition was instituted. Autogenous vaccine, prepared from the dental infection was employed.

## GALL-BLADDER DISEASE

Under this heading are grouped 120 patients who suffered mainly from cholecystitis, a few from the acute form, and 12 cases of cholelithiasis. Although practically every one of these cases has been studied most thoroughly including a roentgenologic dye investigation, the usual difficulties en-

countered in differentiating gall-bladder pathology with stones from that without stones has also here been encountered. However, from the point of view of dental infection it does not matter, since the former is very often the offspring of the latter and both have as a rule an identical etiology. In a few cases the diagnosis was confirmed by surgery.

In gall-bladder disease infection plays an important rôle. Out of 120 patients, each one had lost on the average  $37\frac{1}{2}$  percent of his teeth as compared with over 42 percent in peptic ulcer. In general, whatever has been said under peptic ulcer holds good here. I have seen again and again all symptoms ameliorate or even disappear immediately and quite often permanently upon the complete eradication of focal infection. Under this heading dental infection plays an important rôle. Failure to eradicate focal infection or to remove it completely is frequently responsible for unsuccessful results in the treatment of gall-bladder disease both medically and surgically. I know of no better way of obviating surgery in gall-bladder pathology than by the removal of focal infection. In this disease as well as in peptic ulcer I believe that better and more permanent results are obtained if along with the usual treatment the administration of autogenous vaccine made from the infected focal infection is performed. The injection repeated after an interval of three months usually gives sufficient immunization. As this is, as a rule, a chronic disease, vaccine therapy is particularly suitable. The treatment of gall-bladder disease by this thorough complete method, obtains

quite often results which exceed our fondest expectation.

The following case from actual practice amply illustrates the considerations just made.

G. S., female, 51 years of age had been suffering for over 10 years with periodic attacks of pain over the right side and back and right hypochondrium. Indigestion was a marked symptom, occasional nausea, vomiting and headaches were present. She gave a past history of having had a partial ovarian resection for cyst, operation for retroversion of uterus and for chronic appendicitis with no relief of symptoms. On physical examination she was 35 lbs overweight, her blood pressure was 170/120, her basal metabolic rate was  $-31\%$ , and she exhibited all the objective signs of gall-bladder disease. The gastric analysis, urine, feces and blood, including the Wasserman test were negative. X-Ray examination of the gastrointestinal tract and kidneys was negative. Cholecystography revealed a chronic cholecystitis. Her teeth showed considerable dentistry. She told me that they were "all right" and that they were continuously being looked after by a dentist of repute in whom she had great confidence. Her weight was reduced to practically normal under the proper endocrine therapy and diet. She was placed under the usual medical gall-bladder treatment with indifferent results. A dental check-up was insisted on which showed on roentgenologic examination retained dead roots, dead teeth and several abscesses. Meanwhile one of the teeth became acutely inflamed and had to be extracted. Immediately there was a disappearance of all symptoms and when all the infection was eradicated and autogenous vaccine immunization instituted this stubborn case was promptly cured by medical treatment.

*Comment.* 1. Patients with focal infection are the subjects of frequent operations which in the main are unsuccessful.

2. Not infrequently the doctor is misled by poor dental work. Many dentists do not understand and even

ridicule the importance of focal dental infection

3 When poor results are obtained in the treatment of the above-mentioned digestive diseases re-check your diagnosis and double your vigilance and search for focal infection

4 The eradication of focal infection and subsequent immunization will prevent useless surgery and turn failure into success

## CONSTIPATION

15 patients in this group, each one had lost on the average  $37\frac{1}{2}$  percent of their teeth. This emphasizes the importance of bad teeth in digestion and the production of gastro-intestinal pathology responsible for constipation. The harmful effects of bad teeth in this condition is twofold, namely, mechanical, resulting in faulty mastication and the consequences which follow this, and metastatic dissemination and toxic absorption from the infected dental areas giving rise to the various pathology in the digestive tract which in turn leads to constipation. At times one sees striking results from this disease from the eradication of all focal infection

## APPENDICITIS

49 patients constituting this group who had over 28 percent of their teeth missing were practically all suffering from the chronic type of this disease. More upper teeth were lost than lower and arranged numerically they have the same striking sequence in both jaws, namely, molars, bicuspid, central incisors, with equal losses of the lateral incisors and the canines. This order holds good in all diseases and even in

normal people. From clinical experience I believe there is a definite etiological relationship between focal infection and chronic appendicitis. No treatment is complete whether medical or surgical without thorough eradication of dental infection. The reason why the end results of both medical and surgical treatment are so unsatisfactory<sup>3 4</sup> is because foci of infection are not completely eradicated whether they be in the teeth or elsewhere (See case cited under gall-bladder disease).

## CONCLUSION

1 Office patients suffering from digestive diseases have lost on the average 36.5 percent of their teeth, compared with normal people (see Table II) who have lost 17 percent and with those from the various medical ailments who have lost 32 percent of their teeth (see Table III)

2 There is a definite etiological relationship to a much greater extent than heretofore supposed between focal dental infection and digestive diseases. The removal of focal infection is therefore indicated in its treatment whether that be medical or surgical.

3 So gratifying is the outcome that where unsatisfactory results are obtained, double your search for incomplete eradication of focal infection or be on the lookout for mistaken diagnosis

4 The eradication of focal dental infection will frequently obviate surgery

5 In health or disease more teeth are lost in the upper than in the lower jaw. In digestive diseases this amounts

to 36.4 percent. All teeth are lost in a definite sequence, namely, molars, bicuspids, central incisors, lateral incisors and canines.

6 The administration of autogenous vaccines made from the infected focal areas is a valuable adjuvant in the treatment of digestive diseases

7. Peptic ulcer has a great tendency to spontaneous healing upon the removal of focal infection

8 The unsatisfactory results from the medical and surgical treatment of chronic appendicitis can be frequently

attributed to failure of recognizing and eliminating focal infection

9. The medical treatment of gall-bladder disease is very satisfactory providing focal infection is completely removed and autogenous vaccine administration is practiced

10. The physician is frequently misled by the dentist who is ignorant of and even ridicules the importance of focal infection. Personally examine every dental roentgenogram The co-operation of the dentist is absolutely essential for success in this work

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# Tropical Sprue\*

By E A BAUMGARTNER, M D., *Clifton Springs, N Y.*

**I**N THE past five years we have had 36 cases of tropical sprue here, usually missionaries returned from the Orient. Before that time there were records of 15 cases among our patients. A great deal has been learned from a study of these cases, many papers appearing during this time on various aspects of the disease. We also have published different findings as they occurred in our cases.

We began our study of this condition with no preconceived ideas of any phase of the disease, as a matter of fact in gross ignorance of the entire subject except the name. One attempts generally to keep free of such handicaps to careful study. But in time we absorb and accept ideas that soon may become as pernicious as any preconceived idea.

There are many phases in the study of any disease. One soon becomes more engrossed in one than in another, with at least apparent neglect of other phases equally important. Our sin in the studies of tropical sprue has probably been the common one in this country in medicine of today—over emphasis of the laboratory side. Another

equally common mistake has been too many publications in an already crowded field. However, we believe that our studies have called attention to several (four) points in sprue, and they have resulted either in confirmation of other work or in establishing new points.

There is still no definite knowledge of the cause of this disease. Osler<sup>1</sup> very wisely gave several of the current theories. They may still be considered current. Ashford<sup>2</sup> at first believed his monilia X, (*Monilia psilosis*) was the cause. Recently this author<sup>3</sup>, agreeing with Scott's<sup>4</sup> work on the low blood calcium occurring in some cases, has been inclined to believe some kind of deficiency also is necessary. The British as a whole, like many other workers on this disease, have not taken too kindly to Ashford's monilia as a cause of sprue (Low<sup>5, 6</sup>). We were at first strongly tempted to this view<sup>7</sup>. In our further studies this organism was found in a smaller percentage of cases. It has, however, been found in culture of the stools in 23 of the 36 cases<sup>8</sup> and in 9 others an organism slightly atypical was found. In 16 cases, the most severe and anaemic of the 36, there were positive cultures repeatedly in every case, although in two the organism was not quite typical in that maltose was not fermented. When we began our first culture work on sprue

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\*This paper is written as an introduction and as a summarizing paper to a series of papers from the Clifton Springs Sanitarium and Clinic appearing in various journals in the past five years.

stools we had had no experience in this type of bacteriological study. In our first case we succeeded in growing the *Monilia psilosis*. We have thus in this series confirmed Ashford's work that this organism may be grown from a large per cent of sprue cases

Is this organism only a secondary invader as some (Low) believe? Recent experimental<sup>9 10</sup> work has not confirmed Ashford's<sup>11</sup> and Smith's<sup>12</sup> earlier studies. A few attempts here with feeding the organism to rabbits caused an infestation but no disease. Intravenous injections of sufficiently large amounts of the culture caused early death of the animal with emboli in spleen and liver, causing no sprue. We admit the possibility of the wrong laboratory animal being used, but no others were available. We doubt whether monilia is the true cause of sprue but we feel more certain of our diagnosis if monilia can be obtained by culture from the stools. We have not confirmed the large percentage of positive cultures in pernicious anaemia<sup>13</sup> and psoriasis (unpublished work) obtained by Wood<sup>14</sup>, and Fleisher and Wackowski<sup>15</sup>

The pathology is certainly not specific. We believe the small liver and thin intestinal wall are only evidence of the extreme loss of weight seen in the cases that die of this disease. The translucent edematous serous surfaces<sup>16 17</sup> also are probably results of starvation. The enlarged mesenteric nodes may possibly be due to reaction to monilia. No monilia was found in them in our case, nor in the intestinal wall. Iron pigment, like that found in pernicious anemia, occurred in the liver in our case, but on examination the bone

marrow was hypoplastic. Perhaps Lambert<sup>18</sup> will have found something more definite when he publishes his necropsy cases, certainly Mackie and Fairley<sup>19</sup> in a wider experience than ours, have not

The symptoms and physical findings are classic. The very definite tetany or marked Chvostek and Trousseau signs seen in some cases are pathognomonic under certain conditions

The severe anemia has been noted repeatedly. In our experience the blood picture of the cases with severe anemia differs from that in pernicious anemia in only two points, the Arneth count<sup>20 21</sup> and the few nucleated red cells present. We have found in sprue that the Arneth count is the same as in the normal. In our 16 severely anemic cases only two, like the cases with pernicious anemia, showed a shift to the right in the Arneth count. Both of these had free hydrochloric acid in the gastric fractional tests. In a third case one of two smears counted showed such a shift. This patient had a negative alkaline tide (probable evidence of achlorhydria, Hubbard<sup>22</sup>) and had also a low blood calcium and tetany reactions. Serra<sup>23</sup> found a low Arneth count in 10 cases of sprue, presumably like that in a pernicious anemia, Fleming<sup>24</sup> found the shift to the right in 2 cases as did Krjnkoff in a study of some cases

The icterus index in the tested cases (20) was slightly higher in the more severely anemic patients than in the whole group. Serra found a low index in 6 cases, and Newham<sup>25</sup> a positive Van den Bergh in 7 cases like in pernicious anemia. Fairley and his co-workers<sup>26</sup> found the blood bile pigments low

rather than high as in cases of pernicious anemia. In our work here, too, the icterus index in a group of 10 cases of pernicious anemia has shown a higher figure (16.9) than in our sprue cases with severe anemia (10.6).

What then is the difference in the blood disease of sprue and pernicious anemia? We confirm Fairley and his co-workers that there is, according to blood bile pigments, less evidence of hemolysis in sprue than in pernicious anemia. The bone marrow in sprue does not show the marked hyperplasia seen in pernicious anemia, shown by autopsy<sup>17, 19</sup> and also by the less frequent occurrence of nucleated red cells<sup>20, 26, 27</sup>. As many lobed nuclei are evidence of older neutrophils this points to slow formation or, (and), slow destruction of this type of cell in pernicious anemia. But in sprue the Arnett shift is not to the right, the neutrophils appear like the normal. Is there a toxin acting especially on young granulated white cells in pernicious anemia? The selective action must be very close if we consider these like the erythrocytes arising from the same primordial bone marrow cell.

The low blood calcium sometimes found in sprue cases is definite even though Ashford<sup>28</sup> and Hernandez found this occurs also in other tropical conditions or in many chronic gastro-intestinal states in tropical countries. Certainly our low blood calcium figures have been from our sprue cases, of which almost half (11 of 30 cases) showed low blood calciums, and in four of these very low calcium figures (8). In this we confirm Scott and others who found cases with low calciums. One wonders how closely

this is related to calcium loss from diarrhea. Figures on the number of stools in our cases are not available, and impressions from memory in medicine are not to be relied upon. Studies of the fats in stools were made in a few of our cases, but the figures obtained varied widely. Certainly though, Linder and Harris<sup>29</sup> work shows some relation to fat metabolism. Some quickly acting costive agent might be of value in the case in extremis. We believe parathyroid extract (Collip) helps these cases, it undoubtedly raises the blood calcium<sup>30</sup>. It seems strange that these cases may not respond to intravenous calcium therapy as occurred in Bovaird's case<sup>31</sup>. No response to this treatment was had in one of our cases<sup>30</sup> but most unfortunately for us the patient was no longer under our care. Recently Holmes and Starr<sup>32</sup> have described some sprue-like cases with low calcium figures, which were improved with parathormone.

Thayseen and Norgaard<sup>33</sup> have found a low blood sugar curve after glucose tolerance tests in cases of sprue. Fasting blood sugars were normal in all of our cases tested (21 cases). Gastric fractional studies show as a rule even in very severely anemic sprue patients a normal or occasionally a high acid content. Only 5 of our 16 cases with severe anemia had an achlorhydria (8) although two others had a negative alkaline tide while only two of the 20 cases with secondary anemia had an achlorhydria. Three out of 25 cases in Serra's series showed an achylia. Fairley's cases also rarely showed a lack of free hydrochloric acid. And yet Castle<sup>34</sup> described a sprue case with free hydrochloric acid which was not



efficient when mixed with beef in improving a pernicious anemia patient. His experiments on the effect of gastric contents of the normal individual in improving the pernicious anemia case are now well known.

We found the gastro-intestinal X-ray examination in many severe cases of sprue almost pathognomonic<sup>8</sup>, a dilated, elongated, atonic colon, often with few haustrations occurring so often among the cases in which the diagnosis of pernicious anemia seemed plausible. Such a colon is not seen in the latter disease. This also we have presented as a new point<sup>8</sup>. Holmes and Starr have recently described very similar findings in cases of "non-tropical sprue". Three of their four severely anemic cases had been in subtropic or tropics where sprue is found and sprue has been described as occurring in patients several years after leaving a tropical climate. Hunter<sup>35</sup>, also, mentioned that a dilated colon was found in cases with disturbed calcium metabolism.

The diagnosis of sprue is often difficult but we have found the above points will usually differentiate it from the two conditions most to be confused, pernicious anemia and pancreatic disease. We have not been convinced that tropical sprue and pernicious anemia are the same disease, even when such students as Christian<sup>36</sup>, Reed<sup>37</sup>, and Wood have been arrayed in support of this view. However, Castle's recent work comes nearer than any other proving that the anemia of sprue and

of pernicious anaemia are due to the same factors. We believe the anemia is a severe hypoplastic type but not aplastic as has been inferred by some<sup>28</sup>.

We have found the high protein, low fat, low carbohydrate type of diet agrees with almost all cases. The liver diet used in pernicious anemia cases has been found just as efficient in the sprue patients with severe anemia<sup>38, 39, 40</sup> and a reticulocyte response similar to that in pernicious anemia has been reported. Ashford related that an increase in reticulocytes occurred following the use of his diet without liver, also after using monilia vaccine. We<sup>41</sup> found 9 per cent of reticulocytes in one case in which no liver had been used. Liver has no particular value in those milder cases with secondary anemia. It was often surprising to see how quickly a sore mouth would disappear without any other treatment than the above diet, or how soon a persistent anorexia gave way to a ravenous appetite. Three cases described by Hubbard and the author<sup>42</sup> show that the high protein diet did no further harm to damaged kidneys.

Even if we report 5 deaths in our series of 36 cases<sup>8</sup> we cannot subscribe to the gloomy views in prognosis expressed some years ago<sup>37</sup>. In our experience even the severe cases may be given a good prognosis if not for ultimate complete recovery, at least for recovery to useful life with no more handicap than to avoid certain excesses of diet. A handicap that is cheerfully observed by numerous diabetics.

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# Note on the Systematic Effect of Hydrochloric Acid in Patients with Achlorhydria

By ROGER S HUBBARD, Ph D., *Clifton Springs, N Y*

**P**HYSICIANS who feed hydrochloric acid to patients with achlorhydria sometimes seem to think that they are employing a form of replacement therapy as they do when they inject insulin into diabetics or when they feed thyroid to myxedematous subjects. Such similes are not correct. Hydrochloric acid secreted by the stomach is formed by the gastric glands from material in the blood stream. As a result of this withdrawal of acid ions the reaction of the body fluids tend to become more alkaline. Later the hydrochloric acid is neutralized in the intestinal canal. The ultimate source of the alkali for this purpose is usually the base in the body. Theoretically the amount of base liberated when hydrochloric acid is formed is approximately counterbalanced by the amount of base utilized in neutralizing that acid. The result of these processes is apparently a rhythm of changes in the alkalinity of the body the reverse of those occurring in the stomach. In achlorhydria this rhythm is absent for acid is not formed from the blood stream and therefore no excess base is produced to be utilized later

in neutralizing it. If hydrochloric acid is fed to a patient suffering from this disease it must be neutralized by the body just as any acid or base ingested by a normal subject must be neutralized by his tissues. This process involves changes in the respiration and in the acidity of the urine which can be measured.

In the present note some data upon the acidity of the urine are given to illustrate the effect of feeding hydrochloric acid to patients with achlorhydria. Such figures show only part of the changes which take place, but they serve adequately to demonstrate the fact that rather marked changes in the metabolism can be brought about by giving rather small amounts of acid to such patients.

Case 1 shows a marked contrast between the reactions of two series of urines collected between 7 o'clock in the morning and one o'clock in the afternoon. The first test was done shortly after the admission of the patient, and the second one was carried out about two weeks later after acid treatment had been instituted. The same breakfasts were fed between 8 and 9 o'clock, and all other conditions were as nearly alike as possible, except that 1 dram (3.7 cc) of dilute hydrochloric

\*From the laboratories of the Clifton Springs Sanitarium and Clinic, Clifton Springs, New York.

acid was given with the meal during the second one. The urine was very much more strongly acid during the second test than it was during the preceding one.

Upon Case II a series of tests was run under carefully standardized conditions. Only the factors described below differed during the different periods. Test "A" was carried out when she was first seen. A diagnosis of achlorhydria was made at this time, and she was given a prescription calling for a dram (3.7 cc.) of dilute hydrochloric acid with each meal. Two months later the examination was repeated. The same breakfast was used, and hydrochloric acid was not given during the test period. The result "B" shows a marked increase in the acidity of the urine. In this instance, as in some others seen, the long administration of hydrochloric acid had apparently produced changes in metabolism which persisted when the usual dose was omitted. Test "C" was similar to test "B" except that the patient received her usual dose of 1 dram (3.7 cc.) of hydrochloric acid in a glass of orange juice with the test breakfast. Under these conditions the urine showed a still greater degree of acidity than it did when the dose was omitted. Tests "D" and "E" are similar to test "C" except that the amounts of acid given were somewhat greater. For some days prior to test "D" 2 drams (6.4 cc.) of dilute hydrochloric acid were given with each meal, but on the morning of the experiment only 1 dram was furnished with the breakfast. In test "E" not only was the increased amount of acid given before the experiment, but the dose

taken simultaneously with the breakfast was also 2 drams (6.4 cc.) It is evident that the degree of acidity of the urine roughly paralleled the amount of acid administered. Since the hydrochloric acid was given in orange juice, and since it is known that orange juice forms base in the body when it is used as a food, test "F" in which a glass of orange juice alone was added to the standard breakfast, was carried out. The figures show that the urine was less strongly acid upon this morning than on any other day when the patient was studied. Test "G" was performed as a final control upon the series. The regular breakfast was fed with neither acid nor orange juice added to it. The figures are almost identical with those obtained in test "B"—the first one carried through after the patient had been placed under hydrochloric acid therapy.

Results on Case III are shown to illustrate the effect of a breakfast containing alkaline forming foods fed to a patient who was free from achlorhydria. Experiment "IIIA" gives the average of the reactions found in six tests where the standard breakfast, consisting of a glass of milk, a glass of water, 2 slices of toast with butter, and an egg was fed, test "B" gives the result when the breakfast was made up of orange, grape-fruit, egg, bacon, and coffee. The urinary reaction was much less strongly acid when the fruit was eaten.

Case IV shows the contrast between a test carried out after 4 days upon a base-forming diet selected from standard food tables and one performed after an equal period upon unselect-

ed foods The patient had had achlorhydria for a long time and had been receiving hydrochloric acid regularly for years She took her usual dose with the standard breakfast in each of the two tests It is evident that in experiment "A" which was preceded by alkaline forming foods, the urine was much less strongly acid than in test "B" which followed a period when the diet was more nearly of the usual type

### CONCLUSIONS

Urine strongly acid in reaction is excreted during the morning period by patients with achlorhydria who receive therapeutic doses of hydrochloric acid with the morning meal Sometimes long-continued administration of hy-

drochloric acid is followed by the excretion of a strongly acid urine even when the acid is omitted on the day of the test If alkaline-forming foods (citrus fruits) are given at breakfast time urine of a diminished degree of acidity is excreted during the morning Administration of an alkaline-forming diet may decrease the acidity of urine excreted when hydrochloric acid is given It seems worth while, when patients do not tolerate long-continued hydrochloric acid therapy well, or when they show any signs attributable to a disturbance of the acid-base balance of the body, to combine the therapy directed towards the gastric condition with any alkaline-forming diet to counterbalance the metabolic effect of the ingested acid

CASE	TEST	REACTION OF MORNING URINE SPECIMENS					
		7-8 pH	8-9 pH	9-10 pH	10-11 pH	11-12 pH	12-1 pH
I	A	7.8	7.8	8.0	7.8	7.2	6.7
	B	4.9	5.2	5.1	5.3	5.0	5.1
II	A	5.5	5.5	5.7	5.4	5.6	5.1
	B	5.0	5.1	5.1	5.0	5.0	5.0
	C	5.0	5.1	5.0	4.9	5.0	4.8
	D	4.9	4.9	5.0	4.9	4.7	4.6
	E	4.9	4.8	4.8	4.8	4.7	4.7
	F	5.6	5.5	5.4	6.5	7.1	6.5
	G	5.6	5.1	5.0	5.0	5.0	5.1
III	A	6.0	5.9	6.2	6.5	6.5	6.7
	B	5.5	5.7	6.6	7.6	7.4	6.3
IV	A	6.1	5.6	5.8	6.1	5.5	5.2
	B	5.4	5.1	5.1	5.2	5.3	5.1

# Method for Adjusting the Diet in Diabetes

By CURTIS BRUEN, M D , *New York*

**T**HE treatment of diabetes mellitus is a problem in quantitative chemistry

In functioning the organism exerts a certain output of energy from the metabolism of foodstuffs. This caloric requirement is equal to the basal metabolism, plus a percentage increment for the specific dynamic action of food, and a percentage increment for activity over and above basal. In order to meet this requirement the several foodstuffs must be metabolized in such amounts as correspond to the dietary equation

$$C=41\text{ CH}+41\text{ P}+93\text{ F} \quad (1)$$

in which C represents calories per day, CH, P and F, grams of carbohydrate, protein, and fat respectively, and the coefficients, their respective standard values of calories per gram

The growth and upkeep of tissue call for a supply of its constituents. Ample allowance of protein, more especially during periods of increase, may safeguard against deficiency of whatever amino-acid is requisite. But for maintenance protein intake need only equal the wear and tear quota. The undue stimulation certain of its metabolites exert on the total metabolism makes it economical to keep protein consumption down to the minimum for nitrogenous equilibrium.

Diabetes is primarily a curtailment of the capacity to store and utilize the glucose equivalent yielded in the digestion of carbohydrate and the metabolism of protein and fat. An excessive increase and sluggish or arrested recession of the blood sugar follows its supplementation. It assumes an over-high post-absorptive base level. As often as its fluctuations overflow the renal threshold it spills over into the urine until the threshold concentration is regained.

The maximum glucose equivalent which can enter the blood stream during the absorptive period compatibly with normal disposition might be determined by the use of appropriately graded test-meals and standards. When post-absorptive hyperglycemia prevails, a given glucose yield can only be placed within, at, or beyond the prevailing capacity to metabolize it according as the post-absorptive hyperglycemia is depleted, sustained, or augmented. Such an influx of glucose as is consistent with normally sugar-free urine does not give rise to such fluctuations of the blood sugar as infringe upon the renal threshold.

Glucose equivalent tolerance, whether taken as the maximum which can be normally handled, or as the maximum which can be burned, is then practically an indeterminate quantity.

Still it is in turn skirted, encroached upon, and passed as sugar delays in the blood, accumulates there, and discharges into the urine. By trial it can be made out where a given intake at any one time stands in relation to these criteria. But the limits of normal disposition and of combustion cannot themselves be gauged. They need only be avoided.

In their metabolism protein, carbohydrate, and fat are mutually interdependent. With certain mixtures of the several foodstuffs metabolizing such a molecular ratio is maintained between typically fatty acid and glucose metabolites as just suffices to forestall the accumulation and excretion of acetone bodies. At the threshold of ketosis ketogenic and antiketogenic metabolites oppose each other in equimolecular proportions.<sup>1</sup> Since the average molecular weight of the more common fatty acids is 270 and the molecular weight of glucose is 180, the molecular ratio of 1:1 is equivalent to the weight ratio of 1:5.1, when ketogenic and antiketogenic precursors are calculated as fatty acid and glucose. Since, in the absorption of carbohydrate, the splitting of fat, and the intermediary metabolism of protein, these several foodstuffs yield fatty acid and glucose equivalents in the proportions

$$\begin{array}{rcl} \text{Fatty acid} & 0.46 \text{ P} + 0.9 \text{ F} \\ \hline \text{Glucose} & \text{CH} + 0.58 \text{ P} + 0.13 \end{array}$$

they must be metabolized in such amounts as satisfy the equation

$$\text{F} = 2 \text{ CH} + 0.546 \text{ P} \quad (2)$$

in order to maintain ketogenic-antiketogenic balance<sup>2</sup>

With a protein quota assigned, both the caloric requirement and ketogenic-

antiketogenic balance are met by the metabolizing mixture which corresponds to equations (1) and (2) satisfied simultaneously.

Such a metabolizing mixture provides sufficient calories and avoids ketosis with a minimum glucose equivalent. It is the theoretical limit of insulin withholding. Hypodermic insulin fortifies and reinforces the capacity for glucose storage and utilization. When the glucose equivalent of this metabolizing mixture exceeds the existing capacity for its metabolism it is necessary to establish a new capacity pharmacologically.

Once the formulation is worked out and the calculations are set down it is well to look into how the application squares with what actually goes on.

The protein allowance need not be adjusted to the total nitrogen excretion but may be set at an empirical minimum of grams per unit of body weight for positive balance.

The normal basal metabolism (Chart 1) is subject to known variation. Conditions associable with diabetes alter the basal. The specific dynamic action of a given meal cannot be calculated because it depends in part on the nutritional conditions it encounters in the organism. The caloric demands of activity over and above basal can only be arbitrarily assumed. As a result only a preliminary approximation can be made of the total caloric requirement. This initial estimate can however be readily enough checked or corrected over a period of time in accordance with the declining, constant, or increasing body weight.

With the protein allowance assigned, and the caloric requirement estimated,



a diet may be calculated for ketogenic-antiketogenic balance, and adjusted to the capacity to utilize glucose and the ability to avert ketosis (Chart 2) The threshold test-diet may be liberalized to that extent, which, with the urine sugar-free, gives the best values of blood sugar and blood lipoids If glucose metabolism is inadequate to even the equivalent of the threshold diet, its carbohydrate may be still further restricted under control of urinary tests for the acetone bodies by using values beyond the threshold Ketosis alone makes insulin imperative Or a diet inside the threshold may be used initially and modified in whichever direc-

tion is indicated. Once a suitable maintenance diet is determined its fat may be deleted so that deposit fat replaces it in the metabolizing mixture in order to reduce the body weight

The standard caloric values of ingested foodstuffs are conventional averages which work out reliably taking into account their incomplete availability and absorption

Actual menus are at best planned from approximate tables of food content

Some portion of the food absorbed is not burned It is used as raw material or laid down The non-caloric food of growth and glandular elabora-

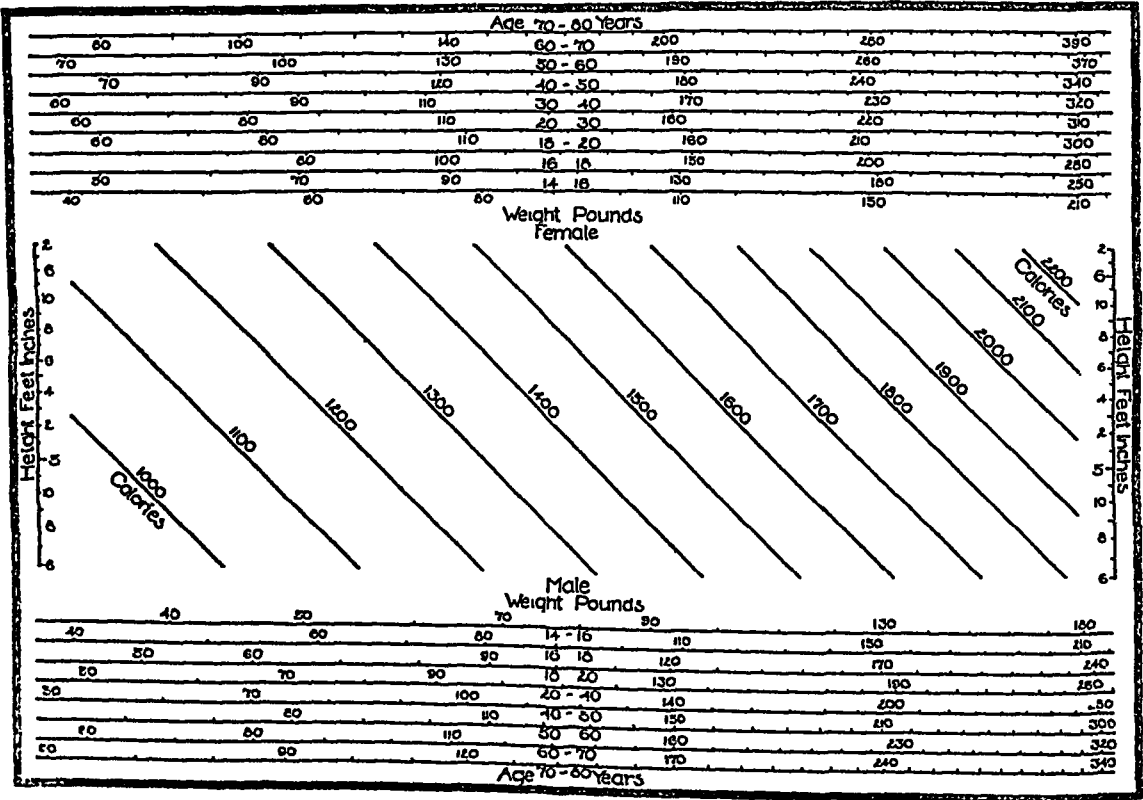


Chart 1—Basal metabolism per day (Du Bois)\* Go to the upper tier of weight scales for females, to the lower for males, identify the scale for the required age group, spot the weight in pounds, carry a line perpendicularly into the field of the chart, spot the height in feet and inches on the nearest scale, carry a line horizontally to its intersection with the vertical line previously traced, approximate the number of calories by interpolating between the adjacent graphs

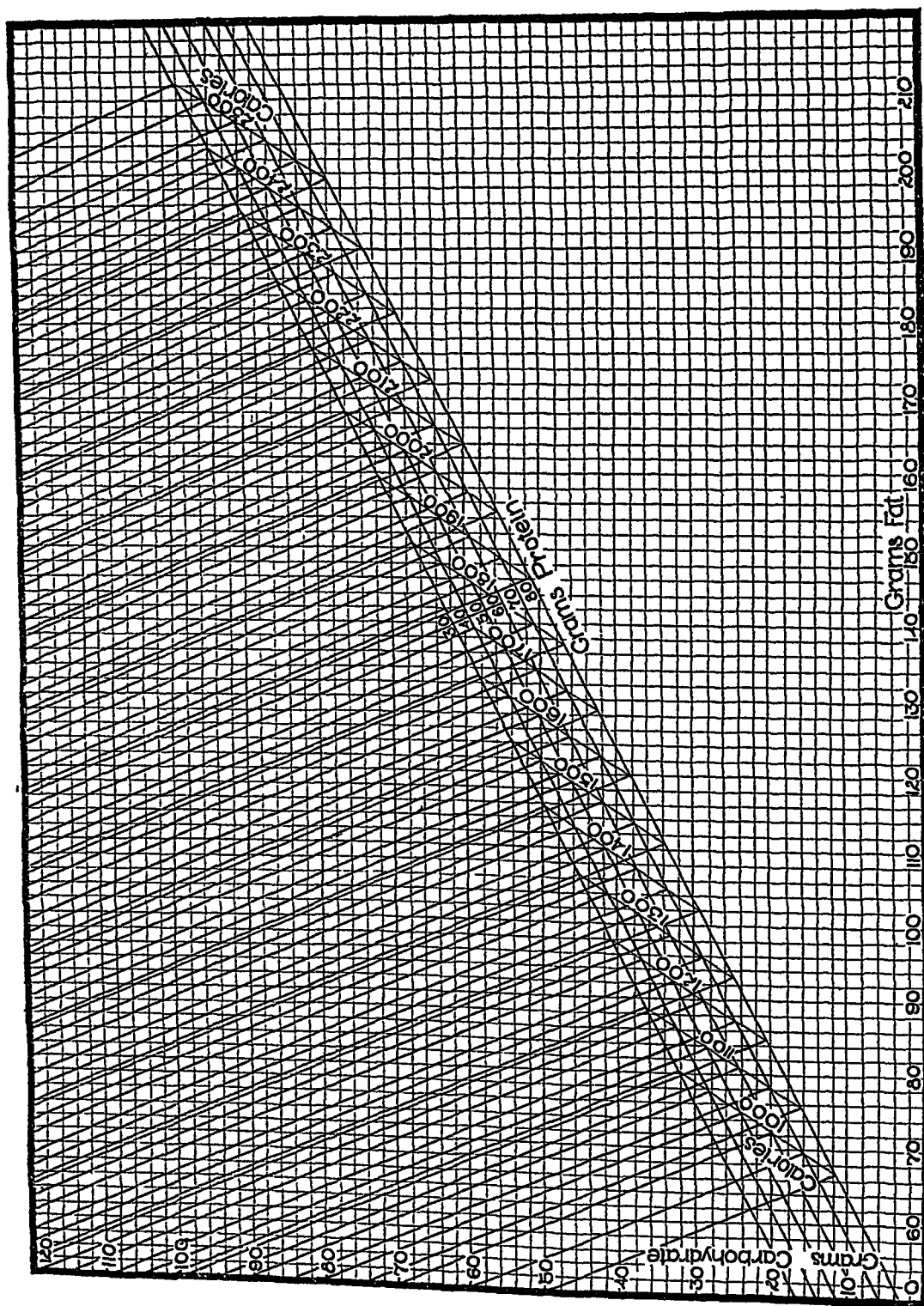


Chart 2—Diabetic diet<sup>4</sup> Identify the graph for the required number of grams of protein, run along it to the point where a member of the bank of graphs for the required number of calories rises from it, read off the coordinates of this point for the number of grams of fat and carbohydrate in the threshold diet, read off the coordinates of points higher up on this graph for diets of increasing carbohydrate, read off the coordinates of points along its projection beyond the intersection for diets of impending ketosis.

tion is outside the caloric equation. It occasions some further discrepancy between caloric intake and output.

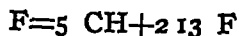
Absorption is not equivalent to catabolism. Yet over a period of time a maintenance diet tends to become a replacement diet. Then ingestion and metabolizing correspond in the gross.

But they cannot agree in detail. The mixture is not completed and absorption does not proceed with the same time relationships for different foods. The absorbed derivatives of the several foodstuffs are independently distributed, accepted into the cells to be processes or loaded there, and remobilized or catabolized as required. Basal metabolism goes on without reference to absorption. The stimulative action of protein metabolites and the plethora effect of those of carbohydrate and fat alter the metabolizing mixture in different ways. Certain foodstuffs are preferentially metabolized in the availability of others. This situation is characteristically modified in diabetes. Not only is carbohydrate metabolism retarded and limited, but fat metabolism is inhibited and curtailed in favor of storage. Conversions among certain of the foodstuffs can occur. On such accounts it is most unlikely that there shall ever be a very close correspondence between the proportions of the several foodstuffs ingested and the proportions of the several foodstuffs metabolized. The only justification for calculating a dietetic mixture with the purpose of establishing a metabolizing mixture is, that, although it ignores all the intermediary factors which may indiffer-

ently augment or cancel each other, it is still more conducive to the intended metabolizing mixture than any arbitrary diet is likely to be. Only on this basis is it feasible to prescribe a diet, which, if metabolized proportionately, would keep metabolism in a certain relationship to the threshold of ketosis.

No uniform metabolic mixture is in fact specific to the threshold of ketosis. Experimental findings<sup>5</sup> vary from the theoretical expectations of ketogenic-antiketogenic balance<sup>1, 2</sup>. But they do not establish any alternative ratio. Rather they plot the extent of deviation from the theoretical. The theoretical formulation remains the only definition available of the metabolic mixture at the threshold of ketosis.

The actual metabolizing mixture may be widely divergent from that of the threshold and still be safe from ketosis. The threshold must be drastically transgressed before any appreciable ketosis develops. Before the production of acetone bodies becomes quantitative there must be in the metabolizing mixture a large preponderance of ketogenic over antiketogenic molecules. When the production of acetone bodies finally comes up to the calculated expectancy it corresponds to the excess of ketogenic molecules over and above twice the antiketogenic molecules. Whereas the threshold ratio is 1:1, the stoichiometric ratio is 2:1<sup>1</sup>, to which corresponds the weight relationships of the equation



So far as the formation of the first abnormal traces of the acetone bodies removed from their production according to the mass law.

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# The Frequency and Clinical Manifestations of Intestinal Worms

By PAUL F WHITAKER, M D , F A C P , *Kinston, N C*

**I**N A former article the writer reported a series of five hundred stool examinations on consecutive patients presenting themselves for study. Since that time a routine stool examination has been continued, and the present paper embraces a series of 1650 cases. This work has been done to determine in a measure the frequency of intestinal parasitic infection in Eastern North Carolina. Some years back the subject was much before the profession, due to the work of the Rockefeller Foundation and enormous good was accomplished through this splendid work, particularly in discovering and treating hook worm infections. At that time one could stand on the street corner on Saturday afternoon in any North Carolina town and diagnose by inspection hook worm infection in the weazened, pasty, listless, and anhydremic faces of people from the rural districts. Now, however, this type of case is seldom seen, and unless the examiner is cognizant of the frequency of intestinal worms many cases are overlooked. It is apparently now a somewhat neglected subject.

The 1650 cases upon which this report is based were private white patients coming through the office or service of the writer at Memorial General Hospital, Kinston, N C. No negro

or child under twelve years of age is included in this series. These cases represent a fairly good cross section of the adult population, many infections being found in the homes of the well-to-do, as well as those in more moderate circumstances, and those from the rural districts. Out of the 1650 stool examinations made, 374 were positive, giving a percentage of 23 per cent infection with some form of intestinal worm. Of this number there were 347 cases of hook worm, 18 cases of round worm, three cases of dwarf tape worm, one case of pin worm, and three cases of beef tape worm. In the cases of beef tape worm the segments and not the ova were found in the stools. Of the total number it can be readily seen, that hook worm is by far the most prevalent parasite, with round worm next in order of frequency. Of the 18 cases of round worm, 8 of these were also infected with hook worm, and two of the three cases of dwarf tape worm also showed hook worm infection. Of the 374 positive cases 204 were males and 170 were females. The oldest positive case was that of a person 67 years of age, the youngest 12. While it is not thought that age is such a significant factor, this point is mentioned for the fact that we believe that the percentage of positive cases would

be ever greater in children than in our series of adult cases

#### HISTORY AND SYMPTOMATOLOGY

A careful history will often lead one to suspect parasites. If asked directly the patient can often be made to recall having had dew poisoning, ground itch or foot itch in childhood or adolescence. Infection with hook worm is usually due to penetration of the unbroken skin by the larvae of the parasite. Sixty-two per cent of the positive hook worm cases gave a history of an eruption on the feet. This percentage would probably be higher if the patient's memory could go back far enough. Some patients can be made to recall having passed by bowel or even vomited so called stomach worms. All three of the cases of beef tape worm noticed the segments of the parasite in their stools. A voracious appetite is supposed to be a prominent symptom of tape worm, but none of these patients had this symptom. Sufferers with pin worm infection frequently complain of intense itching around the anus and vagina.

Weakness, dyspnea, and chronic and early fatigue were complained of by seventy-five percent of the positive cases. The greater the degree of associated anemia, the more marked were these symptoms. Nervousness, vertigo, anorexia, irritability, listlessness and headache are prominent symptoms. Vague digestive disturbances are quite common. We are greatly impressed with the frequency of intestinal worms in the so called neurotic or neurasthenic individual and we believe that this diagnosis will be made less often and with more caution if one

will take the time and trouble to examine the stools. It is gratifying to see the results of treatment in this type of case.

#### PHYSICAL EXAMINATION

The appearance of the patient is often suggestive. The skin and visible mucus membranes are usually pale and suggest anemia. The patient is often but not always underweight. The muscles are usually flabby. In cases of pin worm infection the mucocutaneous junction around the anus and vagina is often reddened and hypertrophied from constant scratching. Slight edema of the ankles with bloating and purplish discoloration under the eyes, without cardiac or renal pathology is a fairly common finding. A mild icterus of the hemolytic type is sometimes present. Hemic murmurs were often found on cardiac auscultation in the more anemic cases. A palpable spleen is no uncommon finding. Thirty-eight per cent of the positive cases had a definitely palpable spleen. There were other patients in the positive series with palpable spleens, but they either had or gave a history of having had malaria, or some other condition that resulted in splenomegaly. These cases are not included in the thirty-eight percent reported. All cases with splenic enlargement had at least a moderate secondary anemia. Why almost forty percent of patients with intestinal worms should have an enlarged spleen is an interesting question. It might be explained as follows. One of the functions of the spleen is to remove crippled or worn out erythrocytes from the circulation. The parasites certainly produce anemia probably by elaborat-

ing a hemolytic substance, which acts on the red blood cells. Granting that this theory is correct the cells rendered useless by the action of the elaborated toxin are removed from the circulation by the spleen in such numbers as to cause splenic enlargement

#### LABORATORY EXAMINATION

In no condition is accurate and properly interpreted blood and stool examinations of more value than in the diagnosis of intestinal worms. The differential blood count revealing an increase in eosinophiles is of inestimable value in leading one to suspect intestinal parasites. Eosinophilia of from 3 to 15 percent is practically a constant finding in hook worm and tape worm infection. Contrary to some observers we believe it to be present in ascaris infection as well. The highest eosinophile count in any case was 15 percent, the lowest 3 percent. The average eosinophile count for the whole series was 5.75 percent.

Every patient with intestinal worms in our series save two had a secondary anemia, characterized by a diminution of red blood cells and hemoglobin. The highest red cell count in any male was 5,020,000, the lowest was 1,340,000; the average was 4,531,000. The highest hemoglobin percentage was 90, the lowest 35; giving an average of 72.6 percent. The highest red cell count in any female patient was 4,360,000, the lowest was 1,000,000, giving an average of 4,140,000. The highest hemoglobin percentage in any female case was 80, the lowest 18; giving an average of 66.3%. Accepting 5,000,000 red blood cells per cubic millimeter of blood as normal in the male, and

4,500,000 as normal in the female with normal hemoglobin percentage as 90 and 80 respectively, there can readily be seen the degree of anemia produced. The presence of eosinophilia in intestinal parasitic disease is interesting. According to Neal and Robnett, eosinophiles are not only present in the blood of patients with intestinal parasitic disease, but are present also in the wall of the intestine. Their presence, like the presence of polymorphonuclear leucocytes in inflammatory disease, and lymphocytes in tuberculosis and syphilis, is intimately bound up in chemotaxis, specific and selective action of the cells for particular irritant micro-organisms and their toxins, and as a response to the need to build up protective antibodies, local enzymes and ferments.

The recognition of the ova of the parasite in question in the stools is of course the final procedure upon which a diagnosis is made. The technique of the stool examination of these cases is as follows: A small particle of the stool is mixed with tap water and shaken vigorously. It is then centrifuged for one minute and the supernatant fluid poured off. Tap water is again added and the mixture centrifuged for one minute. The ova are concentrated in the bottom of the tube, and this material is examined under the microscope. It requires training, skill, and patience to recognize and differentiate the various ova, and this work should be done by one meeting the requirements. Examination of the fecal mass with the naked eye will suffice for the pinworm. Each parasite is about a quarter of an inch in length, colorless, and projects its extremity above the

fecal mass where it moves about slowly like threads waving in the air. A negative stool examination, however, should not deter one from making the diagnosis of hookworm infection where eosinophilia is present, and the symptoms warrant the diagnosis. We have repeatedly demonstrated the presence of ova in the stools after treatment of such cases.

#### TREATMENT

For hookworm and round worm infections a combination of oil of chenopodium and carbon tetrachloride is used in average doses of 30 minims each put up fresh in capsules. This dose is varied in some cases, depending upon the condition of the patient.

For tapeworm infections we have found nothing better than the oleoresin of aspidium in 40 grain doses combined with two drams of spirits of chloroform. Proper purgation of the patient with abstinence from food is essential.

For pinworm infections quassia enemas are used. It takes prolonged and persistent treatment to rid the patient of this troublesome parasite. We treat the patient until a negative stool is obtained, and have found that it takes an average of two treatments to effect a cure.

The treatment of deRivas of Philadelphia is mentioned. He treats a patient by the instillation of physiologic saline solution into the duodenum and rectum, basing his treatment on the assumption that a solution at a temperature of from 45 to 47 degrees centigrade is lethal to the parasite, and at the same time has no ill effect on the intestinal mucosa. Experimental work on animals tends to bear out his as-

sumption. The author has had no experience with this method, but it is quite a common clinical observation that roundworms are often vomited by children with hyperpyrexia, the high temperature probably playing a part in causing the parasite to leave its host.

#### SUMMARY AND CONCLUSIONS

1 Intestinal parasitic disease, particularly hookworm infection, is much more prevalent than is generally recognized and by no means so easily eradicated as is commonly supposed.

2. We believe that careful histories, thorough physical examinations, carefully made stool and blood examinations, with their proper interpretations, offer the best means of detecting these infections.

3 Quite a number of so-called functional nervous patients suffer from unrecognized intestinal parasitic infections, and respond promptly to treatment.

4 A palpable spleen is recorded as a common physical finding in intestinal parasitic disease and the explanation of this finding is attempted. So far as we know, this finding has not before been reported as associated with intestinal parasites.

5 Secondary anemia is practically a constant finding in intestinal parasitic disease. Attention is again called to increase of eosinophiles.

6. Treatment of the various parasites is discussed. Treatment is persisted in until a negative stool is obtained, and it has been our experience that it takes an average of two treatments to effect a cure.

7 In conclusion I wish to thank Miss Mildred Ringle, R. N., technician



at Memorial General Hospital, Kinston, N C, for her assistance in studying these cases from the laboratory

standpoint. Her enthusiastic and accurate work has illuminated the study of these cases.

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# Plasmochin As An Aid in Malaria Prevention\*

By NEIL P MCPHAIL, M D , *Puerto Barrios, Guatemala*

**D**URING the twenty-two years in which the Medical Department of the United Fruit Company has made earnest efforts to reduce the incidence of malaria in the Motagua Valley where they operate, dependence was placed for the first number of years on two main measures

On one hand all collections of water in close proximity to campus were drained when possible, and treated with oil or Paris Green when drainage was impractical. These measures were directed against the breeding of the *Anopheles* mosquito. On the other hand the human carrier was treated with lengthy courses of quinine, arsenic, and other tonic preparations, under as close supervision as possible.

By experience we found that these measures reduced the incidence of malaria very much, and a smaller number of employees developed serious forms of malaria, requiring hospital treatment, and the death rate was much reduced.

In the later years, about 1925 and 1926, when the thick film method of blood examinations was perfected, and in general use, we began extensive blood surveys of the camp labourers and their dependents. A surprising

number of those bloods were found to contain gametocytes, frequently when no trophozoites (ring forms) could be demonstrated.

We then began to examine the bloods of patients about to be discharged from the hospital, in a convalescent state after malaria attacks. We found that an alarming number of those, whose symptoms of fever had disappeared for a minimum of five days, who had excellent appetites, and were demanding to be discharged, carried large quantities of gametocytes in their peripheral blood. This presented a difficult problem, as we found it impossible to clean the sexual forms from the blood by quinine and arsenic treatment in a reasonable time. It meant that we were discharging large numbers of convalescent patients from the hospital, to go back to their camps, to join the ranks of many already there, all in an excellent state to infect mosquitoes.

About this time we had the first opportunity to test the value of plasmochin in the treatment of malaria.

A large series of hospital cases of malaria were placed on plasmochin treatment, and daily blood specimens taken and examined.

The dosage recommended by the manufacturers and sponsors of plasmochin was 9 to 12 centigrams daily.

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\*From the Quirigua Hospital, Puerto Barrios, Guatemala

for six days, and we began with that dose

All cases chosen had positive bloods on admission, and a series were given plasmochin alone, and another series were given plasmochin and quinine together. The most interesting and important development was that in all the cases, in a series of over 100, gametocytes had entirely disappeared from the peripheral blood in five days, and in the majority of cases on or before the fourth day.

Another notable finding was that in cases of estivoautumnal infection the ring forms did not disappear so quickly in those treated with plasmochin alone as in those in which quinine was combined with it.

I will not detail all experimental work carried out, but when we had checked carefully over 1000 cases, we had come to the following conclusion:

(1) Plasmochin had a much more powerful effect in destroying the gametocytes of all forms of malaria than any treatment which we had previously known.

(2) Quinine was much more effective in the destruction of ring forms of aestivoautumnal malaria (trophozoites) than plasmochin.

(3) The ideal treatment in all types of malaria infections was a combination of plasmochin and quinine. With this treatment symptoms were rapidly controlled, the formation of gametocytes effectively prevented, and already existing trophozoites and gametocytes were rapidly destroyed.

The results made it apparent that at last we were able to discharge convalescent malaria cases from hospital with their peripheral blood free from

sexual forms of parasites. In this way we felt we had arrived at another milestone of progress, and returned all hospital cases to their camps unable to infect mosquitoes.

During above experiments we found a small percentage of the cases develop signs of toxicity, before completion of the course. The main symptoms were pain in the abdomen, cyanosis of lips and nails, and occasional nausea. Less than 5% of the patients developed this condition, and all promptly recovered when treatment was suspended. The dosage for adults had been 2 gm. of quinine and 9 centigrams of plasmochin for five days. On account of toxic symptoms occasionally developing we felt that plasmochin, while a valuable aid in hospital treatment, could not be utilized as an aid in field-work, in the dosage recommended.

We undertook a series of treatments, where we gave 6 centigrams of plasmochin instead of 9, and controlled results with daily blood slides.

We were gratified to find that the smaller dose gave identical results with the larger. In a large series of cases we noted that toxic symptoms were practically absent, and we felt justified in believing that we could safely introduce plasmochin, in these reduced doses, to our field work.

Later still (1928) we experimented along similar lines in hospital with a dosage of 3 centigrams daily for six days, combined with two grams of quinine, and careful blood control examination showed that gametocytes disappeared in 4 to 5 days at most. With this dosage we found toxic symptoms were unknown.

At this stage we decided that plasmochin could safely be added to our field dispensary and overseers, stocks of medicines, for use in this dosage, to light cases of malaria who did not wish to come to hospital

At intervals blood surveys are made of all the inmates of our camps, and a list of the positive ones submitted to the overseers. All adults on the list receive 2 grams of quinine and 3 centigrams of plasmochin daily, in 2 doses, for six full days, and children's dosage is worked out according to age and noted on the list

In earlier surveys we checked up all the bloods of those treated, the day after treatment was completed. Results were so uniform, and negative bloods so constant, that we have practically discontinued a second examination and so save the doctors and technician's time. The re-surveys left no doubt at all that the treatment had cleared the peripheral blood of parasites—rings and gametocytes—and for the time being all individuals were unable to infect mosquitoes

When blood surveys were made in camps before we had plasmochin, and treatment given to positives with quinine and arsenic, we found in the re-survey, that in most cases ring forms had disappeared but that we frequently found more sexual forms present in the peripheral blood than we did before treatment. As long as sporulation continues in a malaria attack gametocytes will almost certainly develop, and quinine is unable to prevent this formation, as plasmochin does

With plasmochin at our disposal we have an excellent aid in the prevention of mosquito infection, a safe and valu-

able help in anti-malaria work in the camps

We have learned from experience that we cannot eradicate malaria from large tracts of tropical low-lying lands, such as those occupied by the plantations of the United Fruit Company, with anti-mosquito measures alone

The treatment of the human carrier is a most important measure in any campaign for the reduction, and ultimate eradication, of malaria in a large and scattered community

I have outlined above one of the methods which we have found most useful in attacking the infections carried by the human being, viz, periodic surveys, with rigidly supervised treatment of those with positive bloods. I might add that our practice has been to treat *all inmates* of any camp in which inhabitants are found to be more than 30% positive. This measure has been extremely useful, and has had no resistance from the labourers or their dependents, who now understand that we are trying to help them. It is over two years since we have had to adopt this measure, as we have not had a community show up with 30% infection in that period

Another camp measure which I believe to be our most valuable aid to the reduction of mosquito infection is in the rigid daily round of each room in each camp in the Division by an intelligent administrator or practicante. Repeated medical surveys of employees in the Motagua Valley make it certain that 85 to 90% of all those feeling ill owe their indisposition to malaria infection. When a man, woman or child feels ill he is seen in less than 24 hours after getting ill

Appropriate early treatment with a cathartic, quinine and plasmochin not only prevents the individual from becoming worse, with consequent loss of time and a probable serious case of malaria, but it prevents him becoming a reservoir of infection to the mosquito

Some skilled observers have more recently undertaken a study to determine the minimum useful dose of plasmochin, as regards prevention of mosquito infection from human beings heavily loaded with gametocytes in their peripheral blood

Professors Barber and Kemp who studied malaria conditions in the Motagua Valley some years ago, and Col Whitmore, working in different sections of the Tropics reached the same conclusions, which are of extreme interest to those of us engaged in preventive work. They determined that a dose of 2 centigrams of plasmochin so devitalized the gametocytes in a heavily infected human being that the mosquitoes which were liberally fed on his blood were unable to develop oocysts

When such highly experienced and careful observers are willing to make such a statement I feel doubly sure that we have in plasmochin an ally of vital importance in our fight to reduce, and

finally eliminate, malaria from the low-lying portions of Guatemala

Up to the present we have used in our work in Quirigua 1,388,000 tablets of plasmochin and feel justified in coming to the following conclusions concerning the use of plasmochin in malaria.

(1) Plasmochin effectively destroys the gametocytes of all forms of malaria when given in doses of 3 to 4 centigrams daily for one week

(2) Combined with quinine plasmochin is a safe and sure way of preventing formation of gametocytes during an acute attack of malaria, and the combination destroys all types of parasites

(3) Toxic symptoms need not be dreaded when dosage is limited to 3 centigrams daily for a week or more

(4) We have ample clinical proof to substantiate a tentative statement that plasmochin is of importance as a curative factor in chronic cases which have resisted long efforts at eradication with quinine and arsenical preparations

(5) Plasmochin is a valuable aid, in the hands of a competent sanitarian, to the diminution of mosquito infection, through the undoubted properties which it possesses of causing the devitalization and destruction of malaria gametocytes

## Editorial

### TOBACCO PATHOLOGY

That there has been a great increase in clinical disturbances ascribed to tobacco smoking during the last decade would appear from the increasing frequency in the literature of articles dealing therewith. Particularly in Germany have numerous articles dealing with this subject appeared. Since 1922, Külbs, Hofstätter, Deneke, Fürbringer, Morawitz, Leschke, Kuttner, Frank, and others have published contributions to our knowledge of the clinical conditions due to excessive smoking. In 1924, Hofstätter's monograph on "Rauchende Frau" appeared in Vienna. Külbs reported observations on 456 cases in which definite conditions were ascribed to excessive tobacco smoking. One writer speaks of the increasing smoking-madness, which particularly in the case of women smokers, is bringing an increasing number of patients into the German Polyclinics, whose symptoms are shown to be due to excessive smoking, because they disappear when the patients refrain from smoking, and reappear when smoking is resumed. Much of this Polyclinic material is made up of young individuals, particularly of young women. The great majority of these cases complain of nervous cardiac conditions, neuralgias, emaciation, gastric disturbances with symptoms resembling those of gastric ulcer, sexual disturbances, pains in the lower

extremities, etc. That these conditions vary so greatly in different individuals is easily explainable by individual differences in localized lowered resistance and in the individual differences in tolerances. Some German clinicians, as Lippmann of Hamburg, believe that the harmfulness of tobacco smoking is much under-rated, inasmuch as the symptoms usually disappear under abstinence from tobacco. He advises that in vague and doubtful cases the possibility of tobacco etiology should be borne in mind. Lippmann (*Klin Wchschr*, January, 1931, p 169) discusses the rarer forms of tobacco injury, considering first the effects upon the heart. He is convinced that tobacco has an elective spastic action on the peripheral vessels, and on the coronaries. Angina in smokers is not rare. Külbs found that 13 per cent of his tobacco patients suffered from angina pectoris. Tobacco angina due to spastic coronary contraction affects younger individuals more often than angina due to coronary sclerosis. It has also a more favorable prognosis as it will not occur again if the individual abstains from smoking. Hypertonus and tobacco injury bear no well-defined clinical relation to each other; but a high blood pressure in young individuals may be produced by tobacco. The vascular spasms typical of tobacco poisoning are often the cause of pains in the extremities, which since

Cracot and Erb, have been known as "intermittent limping." Parasthesias and cramps in arms and legs, and also in the head, diffuse or sharply localized, are often seen to disappear by complete abstinence from tobacco. This may be taken as proof of their tobacco etiology. In severe forms endarteritis may be found, but in the milder forms in which the spastic nature is certain, there is rapid relief from the pains, with normal pulse and normal vessels, through abstinence. Intestinal symptoms, due to vagus stimulation, such as constipation, intestinal and stomach cramps, are very common in young smokers. A goodly number of ulcer patients are strong smokers; but many cases suspected to be peptic ulcer disclose themselves finally as tobacco cases. In these cases we often see increase of the symptoms suggesting the picture of a tabetic crisis. These symptoms disappear during periods of abstinence to return when the patient resumes smoking. Cases of gastrosuccorhea may have a neurogenous origin due to tobacco. The more rare forms of tobacco symptoms in the form of coronary spasm, optic atrophy, intermittent limping, acoustic neuritis, gastrosuccorhea, etc., may occur singly or combined in different cases, according to the lowered local resistance and the individual degree of tolerance. Particularly in the case of young women smokers (college girls) does there appear to be a great increase in the occurrence of vague neuralgias and gastrointestinal symptoms. It is well for the practitioner if he develop a suspicious attitude towards the habit of smoking, if it is present, in such patients. An enforced abstinence will sometimes

produce striking cures. Many of our clinicians, confirmed smokers themselves, do not readily suspect the, to them, harmless habit, of being at the bottom of such symptoms; and so fail to benefit their patients. As to the relationship of smoking to cancer of mouth, esophagus, throat, larynx, and lungs, all authorities agree that smoking habits undoubtedly increase the liability to these forms of cancer. Other factors, such as infection, poor dental conditions, burns, mechanical irritation, enter into the production of smoker's cancer. Hoffman believes that the increase in cancer of the lungs throughout the civilized world, is, in all probability, to a certain extent directly traceable to the more common practice of cigarette smoking and the inhalation of cigarette smoke. The latter practice, he believes, unquestionably increases the danger of cancer development. It is still too soon to tell whether the recently acquired smoking habits of women will lead to an increase in the incidence of lip, throat, esophageal, laryngeal, and pulmonary cancer in the female sex, but such an increase appears to be not unlikely.

#### *HAS THE TONSIL AN INTERNAL SECRETION?*

At last, the tonsils, those small organs that to many clinicians seem not only useless but positively dangerous, and made apparently only to furnish employment for their removal, seem to be acquiring a new importance in the minds of some of the continental physicians. That the tonsils are primarily defence organs, even the most ardent believer in tonsillectomy will admit. The function of its lymphoid tissue is

to destroy the bacteria entering through the crypt and surface epithelium. A catarrh of the mucosa leads to a hyperplasia of the lymphatic tissue. The increasing resistance or immunity of the mucosa with advancing age leads to an inactivity atrophy on the part of the lymphoid tissue. Halasz reports eighteen cases of chronic pharyngitis developing in patients after tonsillectomy. The blood picture of these patients showed a leucopenia with a relative lymphocytosis. These patients were given subcutaneous injections of an albumin-free tonsil-extract, made from calves' tonsils. The injections were given daily, in doses of 1 cc (extract of 1 gram of gland). One patient received 12 injections, the other fewer. After the first 1-2 injections the leucopenia was transformed into a leucocytosis, but the lymphocytosis remained more or less unchanged. In all eighteen patients the pharyngeal catarrh was promptly healed. Therefore, it might be regarded as a "pharyngitis tonsillo-priva" due to the lack in the organism of the product of the removed tonsils. Here is an opportunity for the development of a new therapeutic field, or fad.

#### *THE IODINE-DEFICIENCY THEORY OF GOITER*

Johann Holst of Oslo, referring to Hellwig's recent paper in the *Klinische Wochenschrift*, in which the latter mentions the frequent occurrence of goiter in the iodine-rich region of Danzig, goes on to say, that in Norway goiters are also seen which are surely not caused by a lack of iodine. Particularly is this the case in young girls in Oslo, where in general, large

amounts of iodine are excreted in the urine. Recently he and a number of his colleagues investigated a small endemic of goiter on the west coast of Norway, in a region where there was no lack of iodine. In the case of these goiters, iodine had no prophylactic effect, because iodine deficiency was *not* the cause of these goiters. Nevertheless, the fact that endemic goiter not due to iodine deficiency occurs should not be taken as proof, as Hellwig and Liek appear to think, that the theory of iodine deficiency is false. It only goes to show that there are other strumogenous factors than iodine deficiency. One may find in a given region one cause of goiter to be active, while in another region another cause may be present. By far the most common cause of goiter in Norway is iodine deficiency. The nature of the other causes of endemic goiter, we do not know. Since we know that in animal experimentation different forms of deficient or one-sided nutrition can produce changes in the thyroid, it follows that other causes of goiter are probably dependent upon nutritional factors.

#### *ALCOHOL AND POSTERITY*

A Bluhm of Munich has contributed a noteworthy experimental study on the blastophthoric effect of alcohol, which confirms Stockard's experiments with alcohol in this country, as well as those of Weller as to the effect of lead poisoning on the progeny of successive generations. Bluhm concerned herself with the problem whether parental alcoholism produces changes in the posterity that are in a strict sense hereditary, or whether the blasto-



phthoria produced by alcohol is only temporary, disappearing in the course of a number of generations. The experiments were carried out on white mice; 32,300 individuals were employed. Only the males of the first generation were treated by means of alcoholic injections under the skin of the back. These animals received six times a week injections of 0.2 cc of a fifteen per cent alcoholic solution. The method had previously been tried out in experiments lasting three-quarters of a year. Applied to man this amount of alcohol employed would amount to a daily consumption of 105 cc of alcohol for an individual of 70 kg. The first generation consisted of 114 pairs of experimental animals and 114 pairs of control animals. Their progeny were paired in closest incest, and bred to the eighth filial generation. The food consisted of a standardized, abundant diet, with all of the food element well balanced. The investigation concerned itself with the following factors: duration of life, growth, fertility, malformation, and degeneration. The results of the observations were as follows. The prenatal mortality of the posterity was up to the 7th generation signifying higher than in the controls. The progeny of a normal control female and an alcoholic male were shown to have a much less chance of surviving the nursing period than had the progeny of an alcoholic daughter and a normal control son. The same was true for the crossings of uncle, great-uncle, and great-great-uncle. The alcoholism of the great parent prevented a part of the progeny from reaching

the age of fertility and led in the higher ages to a significantly lowered resistance against death. The growth was slightly affected in the male descendants. Paternal alcoholism was able to produce sterility even in members of the seventh filial generation. The increased mortality in the new-born of the descendants of the alcoholic lines is dependent in the first place upon an injury to the genes, which must have its seat in the sex-chromosomes. It is regarded as a defence reaction, which the sperm, damaged by alcohol, excites in the egg, and which in the course of generations leads to an increase of the defence material. Intestinal catarrh played an important rôle in the cause of death. In regard to the occurrence of malformations and degenerations in the alcoholic posterity no difference was noted from that in the control posterity, except for a marked general stunting of the alcoholic posterity. In favor of the genetic significance is the much more frequent involvement of the male descendants, which appear to be the exclusive carriers of the alcohol damage. The importance of this work of Bluhm can hardly be over-estimated. It is the first experimental work in blastophthoria in which proof is offered of direct involvement of the genes or chromosomes, and a definite localization of the injury in the sex-chromosomes. This is, therefore, added experimental proof of the transmission of acquired pathological characters, and has, therefore, most important biologic and eugenic significance.

## Abstracts

*Mercurialism Due to External Use of Mercurochrome* By D E H CLEVELAND (Can Assoc Med Jour, Feb, 1931, p 272)

Most of the adverse reports concerning the use of mercurochrome refer to its intravenous use. A number of reports have been published of mercurial intoxication from intravenous use and also from its application to cavities lined with mucous membrane. Mercurial dermatitis caused by its application to skin surfaces, as is sometimes observed in connection with the use of white precipitate ointment or bichloride lotions, is also known to occur, but few if any cases have been reported of general mercurialism resulting from its use on the skin. Cleveland reports a case showing that the use of mercurochrome as a skin disinfectant is not without dangerous possibilities. In a newborn child, apparently otherwise healthy, the lesions of impetigo contagiosa were treated over a period of 12 days with 4 per cent mercurochrome. About the 7th or 8th day the child began to be salivated, failed to feed properly, and lost weight, apparently due to soreness of the mouth, and on the 11th day developed a generalized erythema. Albumin was found in the urine. All these symptoms subsided rapidly upon withdrawing the mercurochrome. Two months later the child was reported by the mother as being perfectly well. Cleveland regarded the case as one of mercurialism due to the external use of mercurochrome.

*Meningitis During Convalescence from Varicella* By LAIGNEL-LAVASTINE, MIGER and CONSTANTINESCU (Bull et Mem Soc Med des Hôp de Paris, October, 1930, p 1448)

Meningeal reactions have been frequently reported as occurring in varicella, but the case reported here is believed to be the first case recorded in which a fatal meningitis

occurred in convalescence from varicella. The patient was a young man, aged 18, who had apparently a mild attack of varicella. While convalescing from this attack, he developed symptoms of a severe meningitis, with convulsions. Death occurred on the fifth day. The autopsy showed a diffuse purulent leptomeningitis with involvement of the cortex. Tuberculosis was excluded by the bacteriological examination and by the inoculation of guinea pigs, both of which were negative. No other source of the meningitis was found, and the authors look upon it as directly connected with the varicella. Meningitis must, therefore, be regarded as a possible, though rare, complication of varicella.

*Certain Aspects of the Pathogenesis of Angina Pectoris* By J H MEANS (Can Med Assoc Jour, Feb, 1931, p 193)

It is important to bear in mind that the term, angina pectoris, denotes a symptom and not a disease. Its distinguishing features are its paroxysmal incidence, its location in the breast (substernal, more to the left than the right), its relation to effort, and its tendency to end in sudden death. To these may be added as a further essential quality, prompt relief by drugs of the nitrite group. In fact, in doubtful cases, this therapeutic test may be considered the final diagnostic proof (questioned by Herrick). Of pains in the region of the heart which are not to be regarded as angina pectoris, the more important are "fatigue" pain, which is dull aching, or sometimes stabbing, usually over the heart itself. Such pain occurs in a variety of conditions, in young people with neurocirculatory asthenia, in certain persons unduly sensitive to tobacco, in organic diseases of the heart, as in mitral stenosis, and hypertension. Presumably it is evidence of myocardial protest, whether the heart is being driven excessively by nervous stimulation or

by the handicap of organic cardiovascular disease. It differs from true angina in location, incidence, relation to effort, and response to drugs. When occurring in connection with organic cardiovascular disease, at least, it responds to digitalis rather than to nitroglycerine. There is also pain in certain cases of pericarditis and aneurysm, clearly very different from angina pectoris. Then there is the pain of cardiac infarction, which Means regards as essentially the symptom of angina pectoris continued beyond its usually paroxysmal duration and accompanied by other manifestations which the infarction brings about. In other words, instead of attempting to distinguish between cardiac infarct and angina pectoris as two separate diseases, we shall do better if we say that in cardiac infarction angina pectoris of a peculiarly continued sort is a prominent symptom, but the symptom angina often occurs with no infarction of the heart. The theories in regard to angina fall into two main groups—that of its coronary origin and that of its aortic origin. The former is the older and more likely correct view. In the light of present knowledge the latter might almost be dismissed. The coronary theories of angina pectoris center about transient asphyxia of the heart. A spasm of the vessels has been supposed to deprive the myocardium temporarily of an adequate supply of blood (ischemia). That spasm of the coronaries can take place in man has never been proved. Keefer and Resnik have advanced the hypothesis that anoxemia can come about merely through a disproportion between the demands upon the heart and its oxygen supply. If because of suddenly increased work the myocardium needs more oxygen, and the coronaries do not allow it to get it, anoxemia may result even in the absence of any spasm. A similar view has probably been in the minds of other writers who have noted the relation of general metabolic level to the incidence of angina, particularly in cases with over- or under-function of the thyroid. Means would like to use the phraseology that the symptom angina pectoris is evidence of insufficient coronary flow. This state of relativity involves a variety of presumably independent variables, anything that causes a disturbance

in balance between the work the heart has to do and its coronary supply. Means is inclined to agree with Keefer and Resnik that anoxemia is the more likely cause. His conception of relative insufficiency of the coronary flow is best illustrated clinically in anemia and in thyroid disease. The occurrence of angina pectoris in patients with severe anemia is well known. The degree of anemia bears no relation to the incidence of angina among different persons, but if the theory of a relative insufficiency of coronary flow is correct, a close relationship between the occurrence of attacks of angina and the level of the hemoglobin in any given individual should be found. Means cites a case proving this point. In the field of thyroid disease angina is met under two sets of circumstances. First, pain having the classical characteristics of angina may occur in thyrotoxicosis, and disappear after its abolition. He regards this as bearing out the principle of relative insufficient coronary flow, and cites a case to illustrate. The other thyroid situation in which angina may occur is that of myxedema, when thyroid is administered in too large doses. The application of the principle of relative insufficiency of the coronary flow is the same as in thyrotoxicosis. Caution should be exercised against thyroid overfeeding. Another instance of angina pectoris developing as a result of elevation of metabolic rate induced by the administration of a calorogenic hormone is that produced in the case of epinephrine. The increase in metabolism after epinephrine injections takes place at once and reaches its peak in from 20-40 minutes. The average time required for the development of angina coincides after injection of epinephrine fairly closely with the peak of the calorogenic curve. The pain comes on at the time of greatest metabolic demand. Epinephrine also greatly increases the work of the heart. It is small wonder, then, that epinephrine will produce angina in those whose coronaries are less elastic than they once were. Means doubts the propriety of using injections of epinephrine as a diagnostic test in doubtful cases of angina, as suggested by Levine and his co-workers. He regards it as safer to wait for a spontaneous attack and then follow the old custom of observing whether

nitroglycerine will give relief. A totally different but also important aspect of the pathogenesis of angina pectoris lies in the threshold of sensitivity to pain. Individuals vary greatly in this respect. Such variations certainly play a rôle in determining the occurrence of the symptom angina. The difference between colored and white races is pointed out. Means then discusses the neurology of the pain in angina, and the recent theories as to its origin. As to the treatment of angina, when metabolic or hemodynamic factors are present, these can be corrected. In general, it is important to keep the demand upon the coronaries, from the point of view of work performed, within the limit they can stand, but it is equally important to recall and treat the emotional factors which may play a very vital rôle. The psycho-therapy of angina, which may be of a very simple sort, reassurance, encouragement to the patient to do as much as he can within his limit, is a very essential part. The new treatment by sympathetic block, Means believes, is indicated only when attacks are so frequent and severe that the handicap is great.

*Sudden Cardiac Death from Ventricular Fibrillation and Its Treatment* By G. W. PARADE (Zeit klin Med, 1930, p 641)

The symptoms of ventricular fibrillation express themselves in the triad of the sudden onset of symptoms leading to death after a few seconds, with persistence of the respiration. The causes of ventricular fibrillation are electric currents, fear, coronary spasm, sudden increase of blood-pressure in bath, chloroform, digitalis, strophanth, adrenalin, morphine, caffeine, ether, air-embolism, embolism, thrombosis of coronary arteries, infectious-toxic damage of myocardium by diphtheria, typhoid fever, scarlet fever, rheumatic fever, syphilis, Chagas' disease, and angina pectoris. In all cases of cardiac damage following any of these causes, it is important to use cardiazol, quinidin intravenously, heart massage, and artificial respiration. For the prevention of the condition, safe-guarding and protection from all of these causes, and eventually quinidin, are indicated.

*Studies on the Etiology of Rheumatoid Arthritis. I. Bacteriological Investigations on Blood, Synovial Fluid, and Subcutaneous Nodules in Rheumatoid Arthritis* By M. H. DAWSON, MIRIAM OLMSTEAD, and R. H. BOOTS (Proc of the Soc f Exper Biol and Med, January, 1931, p 419).

The clinical evidence pointing to an infective origin of rheumatoid arthritis has led numerous investigators to seek a bacterial agent to which etiological significance could be ascribed. A great variety of such agents has been reported, but lack of uniformity in the results obtained has confused the issue. Cecil, Nicholls, and Stansby, by the use of a special technique, claim to have demonstrated the presence of streptococci in the blood stream in 61.5 per cent of a series of 78 cases examined. Because of the unusual nature of this report and the importance of their findings, the present investigation was undertaken. The greatest care was exercised to follow their technique. The patients selected in all cases presented the characteristic clinical syndrome of rheumatoid arthritis. Cases of hypertrophic and degenerative osteoarthritis were not included. One hundred and five separate blood cultures were done on 80 patients. Repeated blood cultures were done on selected cases. 31 samples of blood were obtained from 16 normal individuals and subjected to similar methods of culture, for control. The results may be summarized as follows. In spite of the greatest care to conduct all manipulations under sterile precautions the technique was so involved as to call into serious question the significance of all bacterial growth encountered. Blood cultures on patients suffering from rheumatoid arthritis failed to yield results which could be considered of etiological significance. No essential difference was found in the variety and character of the bacteria encountered during the culture of specimens of blood from patients with rheumatoid arthritis and of the control material. On two occasions colonies of *Streptococcus viridans* appeared during the culture of specimens of sterile agar subjected to similar manipulations. Twenty-three samples of synovial fluid, obtained from 19 patients suffering from rheumatoid arthritis were cultured both aerobically and anaerobi-

cally on a great variety of media. The cultures failed to yield organisms which could be considered of etiological significance. Careful bacteriologic studies were carried out on a series of 16 subcutaneous nodules from 11 patients suffering with rheumatoid arthritis. Aerobic and anaerobic cultures of these nodules in a wide variety of media failed to yield organisms which could be considered of etiological significance.

*Studies on the Etiology of Rheumatoid Arthritis II Agglutination Reactions with Hemolytic Streptococci in Rheumatoid Arthritis*. By M. H. DAWSON, MIRIAM OLMSTEAD, and R. H. BOOTS (Proc of Soc f Exper Biol and Med, January, 1931, p. 421).

The bacteriological investigations on the blood, synovial fluid and subcutaneous nodules in rheumatoid arthritis reported by those investigators entirely failed to confirm the results reported by Cecil, Nicholls, and Stainsby. The latter had, however, further reported that the sera of patients suffering from rheumatoid arthritis possessed the property of agglutinating their "typical strains" to a remarkably high titre. Through the courtesy of Dr. Cecil several "typical strains" were made available. Specimens of serum were obtained from a large number of patients suffering from rheumatoid arthritis and agglutination tests were done using these strains as agglutinogens. For control purposes a large number of other organisms obtained from a variety of sources was similarly employed against the sera of patients with rheumatoid arthritis. The study was further controlled by utilizing a large number of specimens of serum obtained from patients suffering from both related and unrelated diseases. In addition to the "typical strains" of Cecil, Nicholls, and Stainsby, which, in the authors' experience showed varying degrees of hemolytic properties, cultures of *Streptococcus hemolyticus*, 4 strains including those from scarlet fever, erysipelas, and obtained from the throat of a patient with rheumatic fever, *Streptococ-*

*cus viridans*, 7 strains, *Streptococcus an-hemolyticus*, 12 strains, green diplococci (undertermined), 3 strains, and *Staphylococci*, 5 strains. Specimens of sera obtained from 66 patients suffering from typical rheumatoid arthritis were employed during the course of this study. Control sera were obtained from 50 cases of both related and unrelated diseases. The results of over 1,000 agglutination tests, using 37 different cultures as agglutinogens on 66 cases of rheumatoid arthritis and 50 control cases have led to the following conclusions. In the great majority of cases sera of patients with rheumatoid arthritis possess the property of agglutinating hemolytic streptococci to an extraordinarily high titre. Strains of *Streptococcus hemolyticus* obtained from scarlet fever, erysipelas, and from the throat of a patient with rheumatic fever were agglutinated by these sera to as high a titre as were the "typical strains" of Cecil, Nicholls, and Stainsby. Absorption tests carried out with *Streptococcus hemolyticus* from scarlet fever, erysipelas and the "typical strains" of Cecil, Nicholls, and Stainsby, failed to show an evidence of specificity of the agglutination reaction for the various strains of *Streptococcus hemolyticus* examined. Of the 50 control series, only 2 showed evidence of agglutinins for the strains of *Streptococcus hemolyticus* employed. Of 31 strains of other organisms used none was agglutinated by the sera of patients with rheumatoid arthritis to any significant titre. The present study supports the following hypothesis. Rheumatoid arthritis, in the majority of instances results from infection with *Streptococcus hemolyticus*. The evidence so far accumulated indicates that no specific strain of *Streptococcus hemolyticus* can be considered as the sole etiologic agent. No evidence has been found that the organisms gain access to the circulation or the joint tissues. The suggestion is advanced that the majority of cases of this disease represent the response of the affected tissues to products of *Streptococcus hemolyticus* absorbed from a distant focus.

## Reviews

*Modern Methods of Treatment* By LOGAN CLENDENING, M D, Professor of Clinical Medicine, Lecturer on Therapeutics, Medical Department of the University of Kansas, Attending Physician, Kansas City General Hospital, Physician to St Luke's Hospital, Kansas City, Missouri With Chapters on Special Subjects by a Number of Writers Fourth Edition 819 pages, 95 figures, charts C V Mosby Company, St Louis, Mo Price in cloth, \$10.00

The rapid sequence of editions of this book shows that it has met with a generous reception at the hands of practitioners, and this in turn means appreciation of its practical value. This edition has been carefully revised. The author has not endeavored to add every suggested change in therapy developed since the last edition, but the inclusions and additions are dependent upon the limitations of his experience and his judgment as to what methods are firmly established and supported by scientific evidence. The recent work on the chemistry of the thyroid principle, the use of desiccated swine stomach in pernicious anemia, salyrgan, postural rest in tuberculosis, Calmette's B C G vaccination, undulant fever, ethylene, parathyroid hormone in Paget's disease, and hyperparathyroidism have all been described. The sections on myxedema, diabetic coma, diet in tuberculosis, cisterna puncture, and infantile paralysis have been rewritten. The general plan and purpose of the book have not been changed. It has apparently been found useful to practitioners of medicine. The author has had in mind the problems of the general practitioner, and has encouraged him to make use of methods that unfortunately are believed by many to belong to the so-called specialist. The original plan of his work was to furnish an outline of all the methods of treatment used in internal medicine, diet, drugs, hydrotherapy, blood

transfusion, etc., all in one volume. In this book every department of medical therapeutics is covered, the first part of the book describes the procedure, the second part gives the indications for its application, based upon the principles of physiological pathology. At the end of each chapter, the author has placed a short list of references in English, as more practical for those who may not have access to foreign works of reference. The author has succeeded admirably in his plan. His method of presentation has improved with the successive editions. He shows much practical good sense, as for example, his advocacy of the efficiency of spanking as opposed to psycho-analysis. This book will be very useful to the general practitioner in medicine.

*How It Happened* By ADALBERT G. BERTRMAN, M D, F A C P, 110 pages F. A. Davis Company, Philadelphia, 1931 Price in cloth, \$1.00

This is a presentation of well-known facts in medicine through the medium of unrhymed poetic form, free verse. The poems, of which there are an even hundred, are given proper names for titles, and in many cases are presented in the names of both husband and wife, or of several members of the family. A large variety of medical subjects are treated, such as delay in diagnosis and treatment, incorrect diagnoses, rheumatic fever, appendicitis, tuberculosis, malaria, cancer, diphtheria, adenoids, patent medicines, the Dick test, horse asthma, mumps, and many others. Abortion and venereal diseases come in for as large a share of attention as they deserve. The solid facts are given, and this little book contains much that every layman should know. Each poem is a moral lesson in itself. How much these moral medical lessons gain by being presented in poetical form, it is of course, difficult to say, but they may make

an appeal to certain classes of our society. No one, however, can doubt the earnest motive behind their creation, and the medical facts here presented are sound beyond argument. There are many citizens throughout the country who can gain important knowledge from their perusal.

*The Antiquity of Hindu Medicine and Civilization* By D CHOWRY MUTHU, M D, M R C S, L R C P, Lond., Associate of King's College, London, Consulting Physician, Mendip Hills and Thumbaram Sanatoria. Third Edition. Enlarged. 112 pages. Paul B Hoeber, Inc., New York, 1931. Price \$1.50.

This little volume will serve the reader as an introduction to a brief survey of the antiquity of Hindu medicine and civilization. European scholars have been slow to admit the claims of the Hindus for the antiquity of their civilization. Recent archaeological discoveries in the Punjab and Sind have revealed the existence of a civilization of over five thousand years ago, showing a relatively high degree of luxury and social conditions much in advance of what was contemporary in Mesopotamia or Egypt. The discovery of some specimens of cinnabar in these ruins suggests that these ancient people knew how to extract mercury from this mineral, and indirectly proves the claim of the Hindus to their priority in making mercury. It is probably to the Hindus that we owe the first system of medicine, and the records of Hindu medicine may be traced as far back as the sixth century, B C. The Hindu system of medicine forms a part of the Vedas, dating to at least 4000 B C. Already in India, Vedic Medicine had so far advanced that the followers of the healing art were divided as surgeons, physicians, and magic doctors. The physicians lived in houses surrounded by gardens, containing medicinal plants which they collected and codified. The properties of a new drug were always praised in the Rig Veda, which gives the names of a thousand and one medicinal plants. The surgeons attended the ladies and acted as accoucheurs, giving medicine to relieve pain and suffering. There is an entire hymn of the Rig Veda devoted to the description and treatment of phthisis. In

the Rig Vedic period, there were already signs of an advancement in surgery, midwifery, medicine, therapeutics, child management, and sanitation. In the latter Vedas the medical system takes on a more definite shape. Atharva Veda contains the oldest literary monument of Indian medicine. The Ayur Veda is the oldest systematic work on medicine, and formed the basis of the writings of subsequent medical authors for many centuries. Fragments of manuscripts exist, containing anatomical descriptions of various parts of the body. In the epic period there were two celebrated medical men, Charaka and Susruta, whose books were considered as standard works on Hindu medicine for many centuries, and were revised and re-edited as late as 1550 A D. Charaka's book on medicine is voluminous, containing 120 chapters. It deals with diseases of the heart, chest, abdomen, genital organs, and lower extremities, their causes, symptoms, and treatment. Chapters are devoted to diet, drugs, antidotes, medical instruments, and appliances. Susruta was a great surgeon, and his work is mainly devoted to surgery. He describes 101 varieties of blunt instruments and 20 different kinds of sharp instruments. Most of the modern surgical instruments are but modifications of those used by the ancient Hindu surgeons. Susruta was the first to advocate dissection of dead bodies as indispensable for a successful surgeon. From the time of Buddha, surgery, anatomy, and dissection steadily declined, while chemistry and medicine increased in importance. Based upon relatively slight evidence, the author claims that the Hindus worked out the atomic theory, the evolution theory, the theory of motion, gravity, sound, light and heat, the presence of ether, the humoral theory, and the circulation of the blood, centuries before they became known to Europe. Much can be made out of very little and the modern Hindu has an exaggerated ego when it comes to recounting the achievements of his race. Nevertheless, this very egoism adds a touch of interest to this brief narrative of Hindu medicine, which would be lacking in the cold-blooded and condensed accounts given in the usual history of medicine. The book is of con-

venient pocket size, comparable to those of the *Cho Medica* series

*Cho Medica Physiology* By JOHN F FULTON, M.D., Sterling Professor of Physiology, Yale University 141 pages, illustrated Editor E. B. Krumbhaar, M.D. Paul B. Hoeber, Inc., New York, 1931. Price \$1.50

This is the fifth of the little volumes in red of the *Cho Medica* series. Physiology arose relatively late in the evolution of knowledge, since it depends ultimately upon analysis and reasoning, rather than upon observation and classification. Physiological knowledge derived from experiment began with Galen, who carried out vivisections on dogs, monkeys, and pigs, and studied the structure and functions of nearly every organ in the animal body. He discovered that aphonia followed cutting of the recurrent laryngeal nerve and that hemiplegia resulted from unilateral destruction of the brain. His experiments upon the physiology of the spinal cord rank as classics of physiologic literature. The first chapter is concerned particularly with Aristotle and Galen. In treating of the growth of physiology during the sixteenth and seventeenth centuries the author has found it desirable to follow three main themes: circulation, respiration, and digestion. Thus the unity of three of the most important subdivisions of physiology is preserved, and at the same time the chief personalities can be brought naturally into consideration. Chief attention has been given to the vascular system since all other branches of physiology were dependent upon the settlement of the problem of the circulation. After Aristotle and Galen, Chapter II deals with Harvey and the circulation of the blood, Chapter III is concerned with respiration, and Chapter IV with digestion. Chapter V treats of physiology in the nineteenth century and the use of the teaching laboratories. There is an epilogue "The Trend of Modern Physiology," an appendix "La Physiologie Générale," a short bibliography, and name and subject indices. The growth of neurology and neurophysiology is given but scant mention, as are also biochemistry and biophysics. The author has dealt with the evolution of the main facts of

what is generally termed physiology in the older conception of the term, as expressed by circulation, respiration, and digestion. He has followed the more personal manner of treatment of the subject, believing correctly, that personal details of the lives of the chief actors in the history of physiology make a more appealing tale, and engage more closely the interest of the medical student for whom the book is primarily intended. The author has succeeded in presenting this history in an interesting and readable manner, largely because of the frequently exercised human touch. It is a very good performance, and he may be congratulated upon it.

*Arterial Hypertension* By EDWARD J. STRIEGLITZ, M.S., M.D., Assistant Professor of Clinical Medicine, Rush Medical College, University of Chicago. Attending Internist, Chicago Lying-in Hospital, Assistant Attending Physician, Presbyterian Hospital. Foreword by Rollin T. Woodyatt, M.D., Clinical Professor of Medicine, Rush Medical College, University of Chicago, Chairman Department of Medicine, Attending Internist, Presbyterian Hospital. 280 pages, 21 illustrations. Paul B. Hoeber, Inc., New York, 1930. Price \$5.50.

The present monograph is based upon a series of lectures given at Rush Medical College during the last several years. It represents an attempt to discuss the problems of cardiovascular-renal disease and hypertension in such a manner that the logic of physiologic mechanism may be used at the bedside. The menace of arterial disease with hypertension and the subsequent threat of cardiac failure is apparently increasing, at least, the clinical occurrence of such cases has increased, and in clinical practical work the frequency and importance of arterial disease are constantly being emphasized. Because of their chronicity and asymptomatic nature the significance of the processes of arterial disease have been given inadequate attention in the past. The author lays emphasis upon the etiologic processes of arterial hypertension and upon the physiologic pathogenesis, he interprets all therapeutic procedures in view of their physiologic applications, emphasizing the reasons



and mechanism underlying the processes involved. He prefers the term arterial hypertension to that of high blood pressure, since the latter calls attention to the blood rather than to the vascular structures themselves. Hypertension per se represents a physiologic reaction occurring in disease of the smaller arterioles, and is in itself not a disease. Arteriolar hypertonia is the fundamental change, the increase in intravascular pressure is secondary thereto. The subject matter is treated in nine chapters. The Problem, Anatomy, Physiology, and Pathogenesis of Hypertension, Symptoms of Hypertension, Treatment, Prognosis, Factor of Cardiac Reserve, Factor of Renal Reserve, and Arterial Hypertension in Pregnancy. There is a fairly complete bibliography, and a bibliographic subject index. The chapter on etiology is an excellent survey of the problem, and the author's conclusions are notable for their analytical sanity. Similarly well done is the chapter on Symptoms, that on treatment shows the same high degree of sound sense. Altogether this book constitutes an excellent survey of the subject, and can be recommended to practitioners as necessary to their libraries. It is the most practical and complete resumé of the subject of which the reviewer has knowledge.

*The Right Honourable Sir Thomas Clifford Allbutt, K C B A Memoir* By SIR

HUMPHREY DAVY ROLLESTON, Bart, G C V O, K C B, M A, M D., D Sc, LL D.; Regius Professor of Physic in the University of Cambridge, Sometime President of the Royal College of Physicians of London. 314 pages. MacMillan and Co, Ltd, London, 1929.

This life of Sir Clifford Allbutt was written at the request of Lady Allbutt. From the beginning the author was handicapped by the paucity of personal material. In spite of his manifold activities extending over wide fields and many years, full materials for an adequate and accurate account have not been at hand. He kept very few letters, did not write a diary, or leave any unpublished reminiscences and very few of his early contemporaries are now alive. The resultant biography is, therefore, not much more than a chronological record, derived chiefly from published sources, such as medical and other journals, and from textbooks. Although this record indicates the wonderful energy, versatility, wide sympathies and scholarly culture of this leader of his profession, the work certainly lacks the interest of the human touch. It is bibliographical, rather than biographical. Yet, Sir Humphrey Rolleston has contrived out of relatively meager data to present a readable and interesting picture of Allbutt, and to permit of a sympathetic evaluation of his life.

## College News Notes

Dr Hugh S Cumming (Fellow), Surgeon General of the U S Public Health Association, is the President of the American Public Health Association for the present year

Dr Henry Mason Smith (Fellow), Tampa, is President of the Florida State Board of Health

Dr Felix J Underwood (Fellow), Jackson, Miss, is President of the Southern Medical Association for the present year

One of the endowed hospitals to serve as centers for the treatment of diabetes, as proposed by Dr Elliott P Joslin (Fellow), Harvard University Medical School, will be erected in St Louis

In connection with the forty-seventh annual convention of the Tri-State Medical Association of Mississippi, Arkansas and Tennessee, held at Memphis, February 17-20, the following members of the College were on the program

Dr F T Lord (Fellow), Boston, Mass

Dr Alfred Scott Warthin (Master), Ann Arbor, Mich

Dr William Gerry Morgan (Fellow), Washington, D C

Dr C C Sturgis (Fellow), Ann Arbor, Mich

Col Charles F Craig (Fellow), Washington, D C

Dr G W McCoy (Fellow), Washington, D C

Dr A C Ivy (Fellow), Chicago, Ill

Dr A F Cooper (Fellow), Memphis, is the Secretary-Treasurer of this Association

Dr Henry H Turner (Fellow), Oklahoma City, has returned after spending

three months in postgraduate study of neurology in London and Vienna

Dr T F Abercrombie (Fellow), Atlanta, addressed the Georgia Public Health Association, January 16-17, on "Proposed Public Health Legislation, State and National"

Dr Clyde Brooks (Fellow), formerly Dean of the School of Medicine, University of Alabama, has accepted the post as Professor of Physiology and Pharmacology in the School of Medicine which is now being organized in New Orleans under the auspices of Louisiana State University. The new school will begin its first session next fall with a class of Freshmen and a class of Junior medical students. A new building for the school is now going up on the campus of Charity Hospital, New Orleans

In the February, 1931, Issue of THE AMERICAN JOURNAL OF THE MEDICAL SCIENCES, the following Fellows of the College are authors of articles indicated

Dr H M Winans, Dallas, Texas "Leukemoid Blood Picture in Pseudomucinous Cyst and Papillary Adenoma of the Ovary",

Dr Thomas Fitz-Hugh, Jr, Philadelphia, Pa "Splenomegaly and Hepatic Enlargement in Hereditary Hemorrhagic Telangiectasia"

Dr J Allison Hodges (Fellow), President of the Medical Society of Virginia, delivered an address on "The Medical Practitioner's Interest in Public Health" at the annual meeting of the State Public Health Nurses at Richmond, January 6

Dr. Hodges, with other members of the Committee on Tuberculosis Clinics of the Medical Society of Virginia, including Dr C Lydon Harrell (Fellow), Norfolk, held a conference with officials of the State Board of Health at Richmond on January 19, for the discussion of tuberculosis clinics and the work of the X-ray service of the Department of Health

Dr. Henry A Christian (Fellow), Boston, was the speaker at a dinner, February 16, in connection with the Annual Congress of Medical Education, Medical Licensure and Hospitals held in Chicago

Dr Beverley R Tucker (Fellow), Richmond, was Chairman of the Committee on Arrangements for the 33d annual meeting of the Tri-State Medical Association of the Carolinas and Virginia held at Richmond, February 16-17

Dr Louis Hamman (Fellow), Baltimore, was one of the invited guests who delivered an address and gave a clinic

Dr. Lea A Riley (Fellow), Oklahoma City, was recently reappointed the member of the Council from Oklahoma of the Southern Medical Association by its President, Dr. Felix J Underwood (Fellow), Jackson, Miss

Dr John A Lanford (Fellow) and Dr Daniel N Silverman (Fellow), both of New Orleans, were elected Treasurer and Librarian, respectively, of the Orleans Parish Medical Society at its last annual meeting

Dr Lewellys F Barker (Fellow), Baltimore, was the banquet speaker at the Southeastern Surgical Congress held at Atlanta, March 9-10 Dr. Barker's subject was "The Necessity for Close Relationship Between the Modern Internist and the Up-to-date Surgeon"

Dr William R Bathrust (Fellow), Little Rock, was elected Treasurer of the Pulaski County (Ark) Medical Society at its last annual meeting

Dr. David Riesman (Fellow), Professor of Clinical Medicine at the University of Pennsylvania School of Medicine, has been appointed Consultant to the Committee on the Costs of Medical Care

Dr. Frank Smithies (Master), Chicago, has been elected a foreign member of La Société Médicale des Hôpitaux de Paris

Dr Harold S Hulbert (Fellow), Chicago, discussed the subject of physically and mentally handicapped children at a statewide conference on child health and protection held in Indianapolis, January 15-17

At the annual dinner meeting of the Marlboro County (S C) Medical Society held January 9 at the Marlboro County General Hospital at Bennettsville, the following delivered addresses

Dr Stewart R Roberts (Fellow), Atlanta, Ga

"Thyroid Heart"

Dr Edgar A Hines (Fellow), Seneca, S C

"Progress in Medical Economics"

Dr James B Sidbury (Fellow), Wilmington, N C.

"Vioosterol and Cod Liver Oil in the Treatment of Rickets"

Dr Robert Wilson (Fellow), Charleston, S C.

Clinic on medical cases

Dr Kenneth M Lynch (Fellow), Charleston, S C

"Public Medicine Versus Private Practice"

Dr Carl V Weller (Fellow), delivered an address on "Primary Carcinoma of the Lung," before the Academy of Medicine, of Cincinnati, on February 2, 1931.

Dr. Anton J Carlson (Fellow), of the University of Chicago, addressed the final session, Section I, Committee A, of the White House Conference on Child Health and Protection on physiologic considerations at Washington, February 19-21

Dr George R Minot (Fellow), Professor of Medicine at the Harvard University Medical School, and Dr. William P Murphy, Instructor in Medicine at the same institution, received the 1930 Cameron Prize of the Faculty of Medicine of Edinburgh University in recognition of their work on the treatment of pernicious anemia

Dr Henry A Christian (Fellow), Boston, addressed the Harvard Medical Society, January 13, on "Clinical Classification of Nephritis"

Dr Charles L Brown (Fellow), Ann Arbor, addressed the Oakland County Medical Society at Pontiac, Michigan, January 16, on "Clinical Use of Diuretics"

Dr David Marine (Fellow), Director of Laboratories of the Montefiore Hospital and Assistant Professor of Pathology at the College of Physicians and Surgeons of Columbia University, was the recipient of a gold medal presented by the New York Academy of Medicine, January 7, in recognition of his research into the structure, functions and diseases of the thyroid gland

Dr William Gerry Morgan (Fellow), Washington, D C, spoke before the Lycoming County (Pa) Medical Society at Williamport, January 9, on "Observations on Etiology"

Dr Lewellys F Barker (Fellow), Baltimore, discussed the interrelated functions of the dentist and family physician in preventive fields, January 5, before the joint meeting of the Cleveland Dental Society and the Cleveland Academy of Medicine

Dr Howard T Karsner (Fellow), Professor of Pathologist at the Western Reserve University School of Medicine, Cleveland, has been elected Chairman of the section on medical sciences of the American Association for the advancement of Science

Dr Karsner was one of the speakers on a symposium on medicine and law con-

ducted before the joint meeting of the Cleveland Academy of Medicine and the Cleveland Bar Association on January 6

"Multiple Cares, Costs, Trends and Problems of Today" was the subject of an address given, January 15, by Dr Stewart R Roberts (Fellow), Atlanta, before the Fulton County (Ga) Medical Society

Dr Lester R Dragsteda (Fellow), Chicago, addressed the Chicago Society of Internal Medicine, January 26, his subject being, "Significance of Failure of Reabsorption of Digestive Juices in Some Gastro-Intestinal Disorders"

Dr George E Pfahler (Fellow), Philadelphia, addressed the Philadelphia Urological Society, January 26, on "Diagnosis and Treatment of Bladder Tumors from the Roentgenologic Standpoint"

On January 1, Dr W S Leathers (Fellow), Dean and Professor of Preventive Medicine and Public Health at Vanderbilt University School of Medicine, was appointed a member for a term of five years of the National Advisory Health Council of the U S Public Health Service.

Dr Hugh S Cumming (Fellow), Surgeon General of the U S Public Health Service, presided at a symposium on cancer research held under the auspices of the National Institute of Health, January 7

Dr LeRoy S Peters (Fellow), Albuquerque, N M, delivered a paper entitled, "Cauterization of Adhesions in Artificial Pneumothorax" before the Jackson County (Kans) Medical Society, February 3

Dr Sidney K. Simon (Fellow), New Orleans, has been elected President of the American Society of Tropical Medicine

Dr A G Sullivan (Fellow), Hot Springs, addressed the Pulaski County Medical As-

sociation of Little Rock, February 2, on "Acute Occlusion"

Doctors L C Towne (Fellow), Milton Shaw (Fellow), L G Christman (Fellow) and T I Bauer (Associate), all of Lansing, Mich, held a symposium on Heart Disease before the Livingston County Medical Association at Howell, February 10

Dr B P Stivelman (Fellow), New York City, has recently been promoted to the position of Attending Physician to the Harlem Hospital, and Associate Physician to the Riverside and Jewish Memorial Hospitals, New York City

Dr Joseph G Terrence (Associate), Brooklyn, was promoted, during November, 1930, to Attending Physician to Kings County Hospital

Dr L T LeWald (Fellow), Professor of Roentgenology, New York University, read a paper entitled "Roentgen Evidence of Osseous Manifestations of Certain Types of Anemia, with Special Reference to Mediterranean Anemia" at the annual meeting of the Radiological Society of North America at Los Angeles, December 5, 1930

Dr George Howard Spivey (Fellow), formerly of Gainesville, Texas, has recently become the Director of the Maricopa County Health Unit of Phoenix, Arizona

Dr C C Wholey (Fellow), Pittsburgh, is Chairman of the Allegheny County Division of the Mental Hygiene Commission of the Medical Society of the State of Pennsylvania

Dr Wholey is the author of an article entitled "The Super-Normal and the Emotionally Unstable Child" in the December Issue of the Pittsburgh School Bulletin

In this same journal and the same issue, Dr E Bosworth McCready (Fellow), Pittsburgh, is the author of an article entitled, "The Duty of the School to the Child Requiring Special Attention"

Dr. A. J Bruecken (Fellow), Pittsburgh, addressed the Pittsburgh Urological Association, December 11, on "Clinical Significance of Reactions"

Dr. Oliver T Osborne (Fellow), New Haven, Conn, is the author of an article entitled "Medical Examinations for Life Insurance" in the Medical Journal and Record, December 3, 1930

Dr David Riesman (Fellow), Philadelphia, recently delivered an address on "The Care of the Patient or the Art of Medicine" at the Harvard Medical School. He also spoke before the Academy of Medicine of Columbus, Ohio, on "High Blood Pressure"

Dr Herman B Allyn (Fellow), Philadelphia, has been re-elected Chairman of the Section on the History of Medicine of the Philadelphia College of Physicians. He read a paper on "Oliver Wendell Holmes; His Wisdom and Humor" at the December meeting of the Section

In the December Issue of the American Journal of The Medical Sciences, the following Fellows are authors of articles indicated

Dr David Marine, New York, N Y  
"Remarks on the Pathogenesis of Disease"

Dr Lewis M Hurxthal, Boston, Mass.  
"The Size of the Heart in Goiter. A Teleroentgenographic Study" (with Dr O J Menard and Dr M E Bogan)

Dr L N Boston, Philadelphia, Pa  
"Gastric Hemorrhage Due to Familial Telangiectasis"

Dr Benjamin Goldberg, Chicago, Ill  
"Epituberculosis. A study of Ten Cases for a Period of Over Two Years" (with Dr Benjamin M. Gasul)

Dr William Gerry Morgan (Fellow), Washington, D C, addressed the Los An-

geles County Medical Association, December 5

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Dr O H Perry Pepper (Fellow), Philadelphia, gave the annual Scripps Metabolic Clinic Lectures in San Diego, Calif, January 8-10

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Dr Samuel M Feinberg (Fellow), Chicago, addressed the first meeting of the Chicago Society of Allergy, December 22, on "Historical Aspects of Allergy"

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Dr Wilham A Evans (Follow), Detroit, addressed the Chicago Roentgen Society, December 10, on "Indications for the Results of Surgical Treatment of Pulmonary Lesions as Observed Roentgenologically"

Dr Benjamin Goldberg (Follow), also of Chicago, spoke before the same meeting on "Roentgenologic Aspects of Pulmonary Tuberculosis in Childhood"

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Dr Joseph L Miller (Fellow), Chicago, addressed the Chicago Society of Internal Medicine, December 15, on "Classification, Etiology and Pathology of Chronic Arthritis"

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Dr George R Minot (Fellow), Boston, gave the seventh of a series of afternoon lectures at the New York Academy of Medicine, January 9, his subject being "Treatment of Anemia"

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Dr Joseph C Doane (Fellow), Philadelphia, was elected the President of the American Occupational Therapy Association at New Orleans during the latter part of October

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The Medical Society of the City and County of Denver was addressed, December 2, by Dr William B Yegge (Fellow), Denver, on "Polycythemia", and by Dr Philip Work (Fellow), Denver, on "Multiple Fat Emboli"

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Dr George H Coleman (Fellow), Chicago, and Dr John Favill (Fellow), Chicago, were elected Secretary and Treasurer,

respectively, of the Institute of Medicine of Chicago on December 3

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Dr Oscar B Hunter (Fellow), Chicago, spoke before the Medical and Chirurgical Faculty of Maryland, December 5, on "Progressive Gangrene of the Abdominal Wall"

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The Greater Boston Medical Society was addressed, December 2, by Dr Solomon Strouse (Fellow), Chicago, on "Medical Complications of Pregnancy"

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Dr Elliott P Joslin (Fellow), Boston, delivered the third of a series of monthly lectures before the William Harvey Society of Tufts Medical School, Boston, December 12, on "The Carbohydrates in the Body"

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Dr Torald H Sollman (Fellow), Professor of Pharmacology and Materia Medica, and Dean of the Medical School of Western Reserve University, delivered the fifteenth Mellon Lecture, December 5, on "Clinical Excretion of Mercury", the lecture being sponsored by the Biological Society for Research of the University of Pittsburgh

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Dr Wilbut C Davison (Fellow), Durham, N C, and Dr Walter A Baetjer (Fellow), Baltimore, Md, addressed the thirty-fifth annual session of the Seaboard Medical Association of Virginia and North Carolina at Elizabeth City, N C, December 2-4, on "The Duke Medical School" and "Infectious Arthritis", respectively

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Dr James M Anders (Master), Philadelphia, gave "A Historic Sketch of the Philadelphia County Medical Society" at the Anniversary Dinner to commemorate the eighty-second birthday of the Philadelphia County Medical Society, January 14 Dr Anders also gave a Health Radio Talk, December 30, entitled "Why the Laxy Fails to Preserve a High Standard of Health", under the auspices of the Philadelphia County Medical Society

Dr Carl V Vischer (Fellow), Philadelphia, is co-author with Dr E O Geckeler of "A Clinical Investigation of Chronic Arthritis, with Special Reference to Treatment", which was published in the January number of the Hahnemannian Monthly. This is a detailed report of the research work done by Doctors Vischer and Geckeler on Chronic Arthritis during the past two years. The investigations were carried out in the Arthritis Conference of the Hahnemann Hospital of Philadelphia.

Dr Edward E Cornwall (Fellow), Brooklyn, addressed the Southside Medical Society at Babylon, December 17, on "The Treatment of Pneumonia".

Dr. Carl R Howson (Fellow), Los Angeles, was elected President of the Los Angeles County Medical Association at the annual meeting held on December 18.

Dr Leon T LeWald (Fellow), New York, was elected President of the New York Gastro-enterological Association for the year 1931.

Dr Donald R Ferguson (Fellow), Philadelphia, is the author of an article entitled "Some Problems in Diabetes", which appeared in the December number of the Hahnemannian Monthly. The original paper was read before the Homeopathic Medical Society of the State of Pennsylvania in September.

Dr George G Hunter (Fellow), Los Angeles, was elected President of the Los Angeles Clinical and Pathological Society for the year 1931.

Dr E J G Beardsley (Fellow), Philadelphia, addressed the Sussex County Medical Society at Georgetown, Delaware, on "Common Cardio-vascular Disorders of General Practice", December 12.

Dr. David Riesman (Fellow), Philadelphia, was the speaker at a Postgraduate Seminar of the Philadelphia County Medical Society on January 9, his subject be-

ing "The Failing Heart of Middle Life". Dr E. J G Beardsley (Fellow), Philadelphia, introduced the speaker.

Dr Frank Smithies (Master), Chicago, was elected First Vice President of the American Society of Tropical Medicine on December 30.

Dr H Brooks Mills (Fellow), Philadelphia, was recently elected Consulting Pediatricist to the Northwestern General Hospital.

Dr Mills also recently addressed the Optimist Club of Doylestown, Pa., on "The Child of Today—The Adult of Tomorrow".

Dr Linn J Boyd (Fellow), New York, is the author of an article entitled, "The Constitutional Factor in Disease", which appeared in the January Issue of the Journal of the American Institute of Homeopathy.

The following Fellows of the College are authors of articles indicated, which appeared in the January, 1931, Issue of THE AMERICAN JOURNAL OF THE MEDICAL SCIENCES.

Dr. George R. Minot, Boston, with Stacy R Mettier, M D "The Effect of Iron on Blood Formation as Influenced by Changing the Acidity of the Gastro-duodenal Contents in Certain Cases of Anemia".

Dr Leonard F C Wendt, Detroit, with Franklin B Peck, M D "Diabetes Mellitus A Review of 1073, 1919-1929".  
Dr Moses Paulson, Baltimore, with Justin Andrews, Sc D "The Incidence of Human Intestinal Protozoa, with Especial Reference to Endamoeba Histolytica, in the Residents of the Temperate Zone".

Dr George Morris Piersol (Fellow and Secretary-General of the College), Philadelphia, is the author of an article entitled, "Acute Indigestion", which appeared in the January 3 number of the Weekly Roster and Medical Digest.

Dr John B Hawes, 2nd (Fellow), Boston, is the author of a new book entitled "Talks on Tuberculosis With Patients and Their Friends", being published by the Houghton Mifflin Company

Dr Hawes has been President of the Boston Tuberculosis Association for the past ten years, he is Consultant, Diseases of the Chest, to the Beth Israel Hospital and is a Director of the Massachusetts Tuberculosis League and the National Tuberculosis Association

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Dr C B Burr (Fellow), Flint, was the Chairman of the Committee of the Michigan State Medical Society which has prepared, in two volumes, "Michigan's Medical History" Dr Burr personally contributed chapter on the following subjects the Physician mainly from the Layman's Viewpoint, the American Indian, his Medicine, etc, Physicians with the Early Explorers and Adventurers, Eighteenth Century Physicians, Pioneer and Early Physicians, Therapy Then and Now, Women Physicians, Medical Societies, Extra-professional Activities

The University of Michigan, in accordance with its newly inaugurated plan of granting an honorary degree, M A, to some physician of outstanding ability or accomplishment in that city, at the fall Convocation of students of the medical school, choose Dr Burr for the first such degree to be conferred

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Dr Edgar F Kiser (Fellow), Indianapolis, with Dr C B Bohner, addressed the Indianapolis Medical Society, January 27, on "Incidence of Syphilis in Private Practice, an Analytical Study of 2329 Cases, Based on Serological Tests"

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D Ellis M Frost (Fellow), Pittsburgh, addressed the Allegheny County Medical Society, January 20, on "Differential Diagnosis of Emypema"

Dr C L Palmer (Fellow), Pittsburgh, was chairman of the Program Committee

Dr W Stanley Curtis (Fellow), Boston, is in charge of the Medical Department of the Youngstown Clinic, which was opened last October Dr Curtis was formerly an Associate of Dr Elliott P Joslin (Fellow), Boston

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Dr Walter C Alvares (Fellow), Rochester, Minn, will address the Dallas Southern Clinical Society at their Third Spring Clinical Conference, March 30-April 3

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Dr Ada E Schweitzer (Fellow), Indianapolis, was the Chairman of the Program Committee for the Indiana Conference on Child Health and Protection at Indianapolis, January 15-17

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Dr H S Hatch (Fellow), formerly of Indianapolis, has recently moved to Morristown, N J, to take charge of the Tuberculosis work in that County

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Dr H O Colomb (Associate), formerly of St Elizabeth's Hospital, Washington, D C, is now Director of the Psychopathic Department of the Providence City Hospital, Providence, R I

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Dr LeGrand Kerr (Fellow), Brooklyn, was elected President of the Medical Association of the Greater City of New York, January 19 This Society comprises all of the five boroughs of the City, and meetings are held monthly at the Academy of Medicine in Manhattan, with the exception that one meeting a year is held in each of the four other boroughs

Dr Kerr's presidential address was delivered on February 16, his subject having been "The Physician and his Literature"

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Dr J L McCartney (Fellow), Chief of the Division of Mental Hygiene, Connecticut State Department of Health, has drawn up a chart of averages of "normal" child development This chart is being distributed to parents as an experiment in positive mental hygiene The chart covers the essential points from birth to twenty-one years of age, the five angles of de-



velopment physical, senses and emotion, habits, education, sociability and play

Dr O R Witter (Fellow), of Hartford, Conn, was elected President of the Hartford Medical Society, at the annual meeting, Jan 5, 1931 Dr C Brewster (Fellow), was elected Vice-President The address of the evening was giving by the retiring president, Dr Edward J Turbert (Fellow), who spoke in "Subsidies by the State for the Care of Dependent Sick"

Dr R A C Wollenberg (Fellow), Detroit, addressed the St Clair County Medical Society on the subject of "Skin Cancer and its Prophylaxis", December 16, at Port Huron, Michigan

Dr William J Stapleton, Jr (Fellow), Detroit, gave an illustrated talk before the Saginaw Valley Medical Society, January 20, on "Hospitals and Clinics in Europe"

Dr William Egbert Robertson (Fellow), Philadelphia, Professor of Medicine at Temple University, gave a Health Radio Talk, "The Heart, a Master Pump", on January 20, under the auspices of the Philadelphia County Medical Society

Dr Irving Gray (Fellow), Brooklyn, addressed the Richmond County Medical Society of Staten Island, February 11, on "Recent Advances in Gastro-Intestinal Diseases"

Dr Oliver T Osborne (Fellow), New Haven, Conn, is the author of an article entitled, "Medical Mentor", which appeared in the MEDICAL MENTOR, January, 1931 pages 6, 7 and 8, Volume II, No 1

Dr Logan Clendinning (Fellow), Kansas City, Mo has tendered his resignation as a Regent of the American College of Physicians, as of December 15

Dr Charles G Jennings (Master) and Dr A F Jennings (Fellow) have announced the removal of their offices to the

Charles Godwin Jennings Hospital, 7815 Jefferson Avenue, East, Detroit, Michigan

Dr Fred W Wilkerson (Fellow), Montgomery, Ala, was the author of an article on "Sprue Tested with Liver" in the October, 1930, Issue of the Southern Medical Journal

### NEW LIFE MEMBERS

The following members of the American College of Physicians have subscribed to the Endowment Fund and have become Life Members on the dates indicated

Sydney R Miller (Fellow), Baltimore, Md, January 22, 1931

William H Gordon (Fellow), Detroit, Mich, January 22, 1931

Samuel Weiss (Fellow), New York, N Y, February 4, 1931

James M Anders (Master), Philadelphia, Pa, February 7, 1931

The attention of Fellows and Masters everywhere is particularly called to a pamphlet entitled "The Creation of an Endowment Fund for the American College of Physicians", published and distributed by the President of the College and the Chairman of its Finance Committee during January of the present year This pamphlet discloses the objects and needs of the College for an Endowment Fund, and points out the advantages to members by subscribing to Life Membership All monies received for Life Memberships in the College, including the original initiation fee of such members, are transferred immediately to the Endowment Fund of the College, the principal of which is held intact and invested in securities approved by the Board of Regents, while the income only is available for carrying out the purposes of the organization

### GIFTS TO THE COLLEGE LIBRARY

Acknowledgment is herewith made of the receipt of the following donations of reprints and books to the College Library of publications by members

Dr Oscar W Bethea (Fellow), New Orleans, La

## 4 Reprints

- "The Treatment of Hyperchlorhydria"
- "A Treatment of Pneumonia"
- "Dangers in the Use of Barbituric Salts"
- "Some Suggestions in Physical Diagnosis"

Dr Grafton Tyler Brown (Fellow), Washington, D C

## 1 Reprint

- "Linseed Meal Sensitization"

Dr Warren Coleman (Fellow), New York, N Y

## 1 Reprint ,

- "Studies on the Flora of the Intestinal Tract"
- (With Annis E Thomson, M D & Max Einhorn, M D, F A C P)

Dr Alexander T Cooper (Fellow), Denver, Colo

## 1 Reprint

- "Phrenicoexeresis in Pulmonary Tuberculosis"

Dr Edward E Cornwall (Fellow), Brooklyn, N Y

## 45 Reprints

- "Physiologically Supportive Treatment of Pneumonia"
- "The Management of the Heart in Pneumonia"
- "Management of the Alimentary Tract in Pneumonia"
- "Some Don'ts in the Treatment of Pneumonia"
- "The Conservative Treatment of Pneumonia"
- "On the Use of Digitalis in Pneumonia"
- "What is Strophanthin? A Pharmacological & Pharmacodynamical Survey"
- "The Dosage and Administration of Strophanthin"
- "Milk as a Food for Human Adults"
- "On Eating to the Best Advantage"
- "Coffee in Health and Disease"
- "A Plan of Feeding in Typhoid Fever"
- "The Limitations of Digitalis"
- "Septic Endocarditis Involving the Right Heart"
- "Extrasystoles"
- "Concerning Endocardial Murmurs"
- "A Plan of Rectal Feeding"

## "A Diabetic Dietary"

"When and How to use Nitroglycerin"

"Paroxysmal Tachycardia"

"Intestinal Putrefaction Toxemias"

"Arthritis Deformans and its Relation to Intestinal Putrefaction"

"Clinical Significance of Variations in the Systolic and Diastolic Blood-Pressures and the Pulse-Pressure"

"Pick's Syndrome, with Report of a Case"

"Chronic Tobacco Poisoning and the Circulation"

"Clinical Study of a Case of Chronic Intestinal Toxemia of Severe Type"

"Some Conservative Aspects of Constipation Therapy"

"The Commonest Focal Infection"

"Clinical Study of a Case of Epilepsy Apparently of Intestinal Origin"

"Functional Disorder of the Circulatory Apparatus"

"The Direct Treatment of Heart Failure"

"Remarks on Constipation"

"Medical Notes on Early New England"

"The Prescribing of Diabetic Diets"

"On Living Longer"

"Some Practical Points in the Treatment of Obesity"

"The Remarkable Case of Luigi Cornaro and how he Balanced his Diet"

"A Simple Treatment for Restlessness and Insomnia"

"Alcohol in Medicine"

"The Fundamental Therapeutic Principle"

"Remarks on the Cardiac Arrhythmias and their Identification by Methods Which Are Generally Available"

"A Point in Stomatology"

"Medical Treatment of Gastric Ulcer"

"A Perfect Meal"

"Treatment of Fecal Impaction"

Dr Donald R Ferguson (Fellow), Philadelphia, Pa

## 2 Reprints

"The Clinical Course of Primary Carcinoma of the Bronchi and Lung"

"Clinical Aspects of Massive Collapse of the Lung"

Dr John H Foster (Fellow), Waterbury  
Conn

2 Reprints

"Observations on Trichinosis"

"The Practice of Medicine in China and  
New England with Observations on  
Hypertension"

Dr Hyman I Goldstein (Associate), Cam-  
den, N J

20 Reprints

"Argyria from Argyrol"

"Cancer of the Liver and the Gall  
Bladder"

"Discussion on Blood Pressure"

"Family Obesity, Obesity in Children"

"Gastro-Intestinal Sarcoma"

"Gonococcemia and Metastatic Gonor-  
rhea"

"Heart Irregularities and the Electro-  
cardiograph"

"Meralgia Paresthetica (Roth's or  
Bernhardt's Disease)"

"Mono-Osteitic Paget's Disease of the  
Bones" (with Henry Zuckerman  
Goldstein, M D)

"Newer Therapy of Cardio-vascular  
Renal Disease" (with Leopold Gold-  
stein, M D, and Henry Z Goldstein,  
M D)

"Notes on Meningitis"

"Paget's Disease of the Bones  
(Osteitis Deformans)"

"Pneumococcus Meningitis Case Re-  
ports with and without Pneumonia"  
(with Abelardo Gonzales, M D)

"Primary Malignant Tumors of the  
Liver"

"Primary Nodular Cancer of the Pan-  
creas"

"Primary Sarcoma of the Appendix"

"Recent Advances in Treatment,  
Angiomy in Angina Pectoris, and  
Hypertensive Conditions"

"Serum Disease"

"Sore Throat and Diphtheria"

"Sporadic Cretinism"

"Wells Disease or Icterus Gravis  
(Acute Infectious Jaundice)"

Dr Ralph O Clark (Fellow), New  
York, N Y

1 Reprint

"Vaccines Their Use in the Control  
and Cure of Disease"

Dr Joseph R Darnall (Associate), Wash-  
ington, D C

5 Reprints

"A Case of Chloroma of the Sacrum"

"Modern Conception and Rational  
Treatment of Diabetes Mellitus"

"Dietetic Management of Cardiac, Vas-  
cular and Renal Diseases" (2 copies)

"The Application of Occupational  
Therapy to Chronic Medical Cases"  
(2 copies)

"Diet in Heart and Kidney Disease"

Dr W Forest Dutton (Associate), Ama-  
rillo, Texas

4 Reprints

"Parenteral Medication"

"A Clearing House for Trite Pa-  
pers"

"The Future of Medicine"

"Progress in Chemotherapy"

Dr Samuel M Feinberg (Fellow), Chi-  
cago, Ill

11 Reprints

"Household Objects as Causes of Hy-  
persensitiveness"

"The Nonspecific Diagnosis of Allergic  
Disease Further Observations"

"Clinic of Dr Samuel M Feinberg—  
"Asthma Due to House Dust"

"Hay-Fever Treatment"

"Progress in Hay Fever"

"Seasonal Hay Fever Not Due to  
Pollen"

"The Vital Capacity in Bronchial  
Asthma"

"The Nonspecific Diagnosis of Allergic  
Asthma"

"Nasal Allergy as Related to Hay Fever  
and Hyperesthetic Rhinitis"

"The Management of the Asthmatic"

"The Relation of Asthma to Broncho-  
Pulmonary Infections and Inflamma-  
tions"

Dr Murray B Gordon (Fellow), Brook-  
lyn, N Y

6 Reprints

"The Effect of External Temperatures  
on the Sedimentation Rate of the  
Red Blood Corpuscles"

- "Morphological Changes in the Endocrine Glands in Mongolian Idiocy with Report of Two Cases"
- "An Endocrine Consideration of von Recklinghausen's Disease Report of a Case with Associated Childhood Myxedema"
- "Cholesterol and Lipoid Phosphorous in Infancy and in Childhood"
- "The More Embrace Reflex in Infancy"
- "Differential Diagnosis Between Diphtheria and Oral Lesions of Blood Dyscrasias" (with Dr Abraham M Litvak)
- Dr John W Meehan (Fellow), Washington, D C  
1 Reprint  
"The Army Medical Center"
- Dr Oliver T Osborne (Fellow), New Haven, Conn  
1 Reprint  
"Medical Examinations for Life Insurance"
- Dr Edward O Otis (Fellow), Exeter, N H  
1 Reprint  
"The Prevention of Disease"
- Dr William D Reid (Fellow), Boston, Mass  
1 Reprint  
"Pregnancy and Heart Disease"
- Dr J, W Torbett (Fellow), Marlin Texas  
1 Reprint  
"Classification, Diagnosis and Treatment of Arthritis"
- Dr Edgar F Kiser (Fellow), Indianapolis, Ind  
1 Reprint  
"Ceremonial Circumcision"
- Dr L J Moorman (Fellow), Oklahoma City, Okla  
8 Reprints  
"Evil Results of Indiscriminate Removal of Tonsils in Adults"
- "Tuberculosis in Medical Curricula"
- "Teaching Medical Students the Normal Body"
- "Recent Progress in the Treatment of Pulmonary Tuberculosis"
- "The Relation of Advanced Pulmonary Tuberculosis to Manifest Tuberculosis in Infancy and Early Childhood"
- "Our Debt to Aristotle"
- "Massive Collapse (Atelectasis) of the Lung, with a Case Report"
- "Tuberculosis and Genius as Manifested in St Francis of Assisi"
- Dr Oliver T Osborne (Fellow), New Haven, Conn  
1 Reprint  
"The Cost of Medical Care"
- Dr Aaron E Parsonnet (Fellow), Newark, N J  
1 Reprint  
"Postinfluenzal Sinus-Nodal Block"
- Dr Virgil E Simpson (Fellow), Louisville, Ky  
4 Reprints  
"Diseases of the Cardiovascular System Due to Acquired Syphilis"
- "Tularemia"
- "Food Content with Relation to Density and Composition of Stone in Upper Urinary Tract" (with Dr Owsley Grant)
- "A Discussion of the Probable Etiological Relationship Between Peptic Ulcer and Vagotonic Syndromes"

## OBITUARY

Dr Archibald Neil Sinclair (Fellow), Honolulu, Hawaii, died October 21, 1930, of heart disease, aged, 59 years

Dr Sinclair was born in New York City, but early went to Hawaii where he received his preliminary education at Oahu College. He later attended Glasgow University from which institution he received the degree of Bachelor of Medicine and the degree of Master of Surgery in 1894. During 1916 he did postgraduate study in roentgenology, pathology, bacteriology and blood chemistry at the New York Post Graduate Medical School. From 1901 to 1919, Dr Sinclair was Assistant Surgeon in the U. S. Public Health Service. At the time of his death, he was Medical Director of The Leahi Home, and bacteriologist of the Board of Health of the Territory of Hawaii.

Dr Sinclair was a member, ex-secretary and ex-president of the Medical Society of Hawaii, ex-secretary and ex-president of the Territorial Medical Association, ex-secretary of the Honolulu County Medical Society, a member of the American Association of Bacteriologists, a member of the American Association of Immunology, a member of the National Tuberculosis Association, a Fellow of the American Medical Association, and a Fellow of the American College of Physicians. He was elected to Fellowship in the latter organization on February 8, 1921, and had served on its Board of Governors for several years.

Dr Charles Bowman Bacon (Fellow), Brooklyn, N. Y., died December 10, 1930, aged, 61 years.

Dr Bacon was born at New Lebanon, N. Y., received his preliminary education at Mount Hermon (Mass.) School and at Cook Academy, Montour Falls, N. Y. He completed two years academic study at Colgate University, and then entered the University of Buffalo School of Medicine, from which he received the degree of Doctor of Medicine in 1897. He interned at Kings County Hospital, 1898-99. From 1905 to 1909, he was visiting physician to the Swedish Hospital, from 1902 to 1909, assistant visiting physician to the Kings County Hospital. Later he was clinical instructor in medicine to seniors from Long Island Medical College. At the time of his demise, he was lecturer in medicine on the staff of the Homeopathic Medical College and Flower Hospital, and medical administrator in the hospital service of the City of New York, Department of Public Welfare.

Dr Bacon was a member of the New York County Medical Society, New York State Medical Society, the American Medical Association, and had been a Fellow of the American College of Physicians since February 22, 1937.

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DR WILLIAM DUFFIELD  
ROBINSON

Dr William Duffield Robinson was born at McConnellsburg, Fulton County, Pennsylvania, March 25, 1856. His

ancestry was remotely Scotch-Irish, his parents were John and Mary (Duffield) Robinson. He received his early education in the common schools of his county and later (1872) graduated from the Chambersburg Academy. Coming to Philadelphia he graduated from the Philadelphia College of Pharmacy in 1876. The subject of his thesis was "Tinctura Cinchonae Composita". In 1880 he graduated from the Medical Department of the University of Pennsylvania. Dr. Robinson entered upon the practice of medicine in Philadelphia and soon thereafter was appointed Resident Physician to the Eastern Penitentiary, serving faithfully for many years. On October 22, 1891, he married Elizabeth T. Willian, who survives him, together with his four sisters.

In 1914 Dr. Robinson was elected President of the Philadelphia County Medical Society and during his incumbency of that office appointed not less than eighteen standing committees with definitely assigned duties. These added activities have been and still are advancing and broadening the work and influence of the society, more particularly in the fields of public and preventive medicine.

"At the outbreak of the World War he instituted the Senior Military Medical Association with Dr. W. W. Keen as President. This led to the formation of the Volunteer Medical Service Corps of the United States which was approved by the Council of National Defense in 1918. The object of this Corps was to 'mobilize the medical profession in the present emergency in order to provide for the

health needs of the military forces and civil population of the country'. Dr. Robinson was one of the members of the Central Governing Board."<sup>1</sup>

He was an ardent advocate of organized medicine and up to the time of his passing, a regular and interested attendant upon medical society meetings, he felt it incumbent upon himself to become acquainted with the facts and deeper questions involved as far as possible, of practical and scientific medicine. Dr. Robinson possessed a strong civic spirit as shown by his performance of an enormous amount of work in the interests of the public welfare. He was an active member and Treasurer of the Better Homes Committee of Philadelphia, a member and Treasurer of the Committee on Arrangements for Public Health Day in Philadelphia for many years, he was a member of the Board of Directors of the Pennsylvania Tuberculosis Society, and for a time served as Vice-President, and for many years he served as a member of the Board of Directors of the Oncologic Hospital of Philadelphia. Dr. Robinson also rendered efficient service to his alma mater, the Philadelphia College of Pharmacy and Science, as a member of its Board of Trustees. He was Chairman of the Medical Board of the Sesqui-Centennial International Exhibition.

Dr. Robinson held membership in many local and national medical societies, for example, in the American Medical Association, the Medical Society of the State of Pennsylvania,

<sup>1</sup>WILMER KRUSEN, M.D., in 'The Weekly Roster and Medical Digest, February 7, 1931

the Philadelphia County Medical Society (vide ante), the College of Physicians, the Medico-Legal Society, and was an extremely active member of the Philadelphia Psychiatric Society. He also served as President of the American Climatological and Clinical Society, the Philadelphia Medical Club (1924), and the Philadelphia Clinical Society.

Dr Robinson was Chairman of the General Committee of the National Pasteur Centenary celebration — a magnificent tribute to that true pioneer scientist, the founder of the germ theory of disease. He thus rendered a notable service to the memory of one for whom he had unbounded admiration. He had marked executive ability and it was one of his chief delights to head a committee and lead in planning a celebration in honor of a colleague or some great historic event. He was an interested member of The Sydenham Coterie of Philadelphia—a body of widely known members and specialists of the medical profession holding monthly dinner meetings. For this small group he had “a peculiar affection” and he attended one of its meetings just three days prior to his untimely death.

During committee meetings, which Dr Robinson faithfully attended, he manifested great resourcefulness in making practical suggestions. His industry was phenomenal, his sympathies were quick and broad, his personality was forceful and ingratiating, his loyalty to friends and his ethical standards were unquestioned and his bearing was always courteous and dignified. These qualities made him popular and greatly endeared him to his

many lay and professional friends. He was a keen clinical observer and throughout his long professional career followed general medical practice. There is always the risk of unjustifiable asperity in one's judgment of the character of another. It was, however, obvious to those who had an opportunity to trace the developments of Dr Robinson's character, that he ever sought to achieve what he did not seek for his own sake, but for the good of others—of society. In the death of the subject of this memoir the medical profession has lost a worthy representative, his friends, an agreeable, magnetic, loyal and much beloved comrade. In him the affable, wise physician and sympathetic friend were happily combined.

If space permitted, interesting personal reminiscences revealing Dr Robinson's capacity for friendship, his versatility and everyday humanity, could be related. Right up to a few days before his passing away, he enjoyed telling stories and relating amusing anecdotes, while time was blotted out for his listeners. It is not too much to say that he radiated good cheer and inspiration to any group in which he found himself, and it is equally true that he gave impetus to the many good causes with which he was identified. It may indeed be said that his indefatigable labors were accompanied with an unusual degree of pleasure, amounting to

“The consummation of all earthly bliss,

The full fruition of a kingly crown”  
(Furnished by James M. Anders,  
M. A. C. P., Philadelphia, Pa.)

# Insulin Angina

## The Development of the Stenocardial Syndrome Following the Administration of Insulin in Diabetics with Coronary Thrombosis

By AARON E. PARSONNET, M.D., *Newark, New Jersey* and  
ALBERT S. HYMAN, M.D., *New York City*

PROBABLY no remedy in the past generation has received as much attention from every conceivable angle as has that of insulin. Since its introduction by Banting, McLeod and Best in 1923, the entire treatment of diabetes mellitus has revolved around indications, contraindications, dosage and numerous other phases of insulin administration. In the six-year period from 1923 to 1929 there are listed in the Quarterly Cumulative Index Medicus more than 1,000 articles concerned with insulin therapy. It is, therefore, inevitable that in the chaotic wake following the introduction of methods of such a decidedly revolutionary scope that many conflicting views and opinions should arise.

No better example presents itself than the present controversy in regard to the proper management of that group of diabetic patients suffering from such cardiovascular complications as myocardiosis, angina pectoris and coronary arterial disease of greater or lesser degrees of severity. The clinical picture of the middle aged individual with a long previous history of diabetes held more or less in check

by a moderate though not absolutely scientific dietary regime who is suddenly projected from a state of hyperglycemic complacency into the throes of an acute coronary attack following an injection of insulin is, by now, a not unfamiliar incident. To many such individuals, the development of this stenocardial syndrome is a new and obviously not a pleasant experience, to the doctor, however, this may be a totally unanticipated complication fraught with sinister possibilities.

The constant factor of glycosuria coupled with the difficulty entailed in securing blood chemistry information by the rank and file of the profession stimulates the desire for a therapeutic shortcut and amelioration of the more obvious diabetic symptomatology. Failing to achieve a sugar-free urine through dietary measures, the temptation to resort to this powerful agent is overwhelming and it is small wonder, therefore, that insulin enjoys such a wide-spread and, perhaps, promiscuous usage. No one is more cognizant of this fact than Banting himself, who in a recent conversation with one of us at the University of Toronto stressed



the fact that diabetes, today, is a much overtreated disease

The association of diabetes with degenerative changes of the vascular system has long been known, hypertension, arteriosclerosis, thromboangitis-obliterans, and many other trophic disturbances of circulation are but a few of the familiar pathologic concomitants of this metabolic disease. Apparently, the entire arterial tree from its very source at the aorta to the terminal filaments of the capillary circulation may be involved as a result of the chemical imbalance engendered by the diabetic syndrome. The coronary arteries are no exception and in many instances seem to bear the brunt of altered pathology.

The incidence of diabetes in coronary thrombosis is relatively high, Levine in a recent study of 145 cases found that about 24% were suffering from various degrees of diabetes. Other authors have also reported figures closely approaching these. In our series of 89 cases of coronary thrombosis there were 22 patients with definite diabetic symptoms. Of this group of 22, seven had severe coronary seizures following the administration of the initial first day dosage of insulin. A review of these cases is interesting in pointing out the difference of clinical response to this substance in individuals suffering from coronary arterial changes in contrast to those running an otherwise uncomplicated diabetic course. We have been impressed beyond a doubt with the ill effects of insulin in such cases as far outweighing the temporary benefits to be expected in mitigating the course of diabetes, in fact, we have seen one fatal

instance and several almost fatal results following its use. A resumé of certain typical cases is herewith presented.

*Case 1* Man, aged 52, salesman, was known to have diabetes for about nine years, having been rejected for insurance because of glycosuria at that time. With no serious attempt to live up to a rigid diet, the patient was seen from time to time by his physician and at the end of eight years at the age of 51, he moved his residence to another city. Some time later, after having had several severe headaches, he went to a neighborhood physician, who after examining him said that he was suffering from a severe form of diabetes and suggested immediate use of insulin. The patient consented and was given an initial dose of 20 units at nine o'clock in the morning. He received the second dose of 15 units at one o'clock. At 2:30, while walking in the street, he was seized with a terrific stenocardial attack and with difficulty was carried home.

When seen by one of us about two hours later, he presented a typical picture of an acute attack of coronary occlusion. The patient was in extreme shock with a cold damp skin, the ashen pallor of the condition was well defined. The heart itself did not seem to be enlarged, the heart sounds were weak, rapid and distant, and at times a definite irregularity was discovered. The blood pressure levels were markedly reduced, averaging about 85 systolic and 40 diastolic. In view of the marked prostration and the extreme pain, only large doses of morphine were given and the patient treated according to the method already described by us. A blood sugar taken on the following day showed 118 mg while the urine was sugar-free. This stands in contrast to a report dated 14 months previously which showed a blood sugar of 210 and a urine analysis made at the same time showed a sugar content of 12 per cent.

After a very stormy convalescence, extending over a period of about five weeks, the patient underwent a complete cardiovascular survey, the salient feature of which was the discovery of an increased left ven-

tricular diameter as determined by orthodiagraphic x-ray examination. Electrocardiographic studies (Figure 1) showed the characteristic T-wave alteration seen in advanced coronary disease.

His blood pressure levels had risen slightly to systolic 100 and diastolic 60. The heart sounds, while of somewhat better quality, were still distant and showed impaired resonance. Vital capacity estimations revealed a marked loss of myocardial reserve. Of special interest was the laboratory report in regard to his blood and urine; the blood sugar level had now risen to 205 mgs

while the urine showed about 1% of sugar. Although somewhat weakened by his experience, the patient had no symptoms referable to his cardiovascular system and was rather comfortable.

For about eight months the patient appears to have been free from any cardiovascular symptoms, at the end of this period he began to be bothered with a left inguinal hernia. This he was advised to have repaired, the surgeon suggesting a preoperative course of insulin therapy in order to reduce the rather high blood sugar. The patient was admitted to the Hospital and temporarily

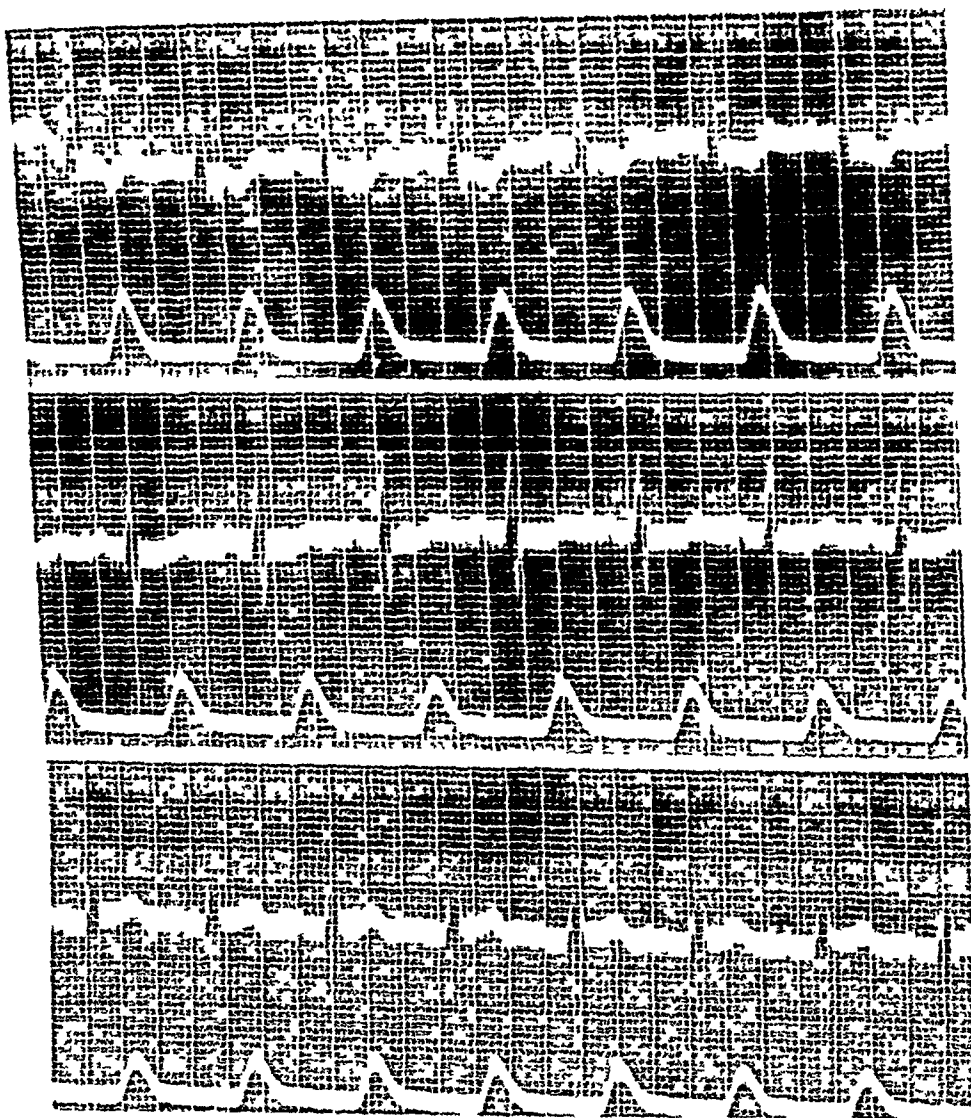


FIG 1 Electrocardiographic and Polygraphic Studies made March 7, 1928, after a first coronary attack. Note T-wave alterations in the first and second leads and the marked left axis deviation of the heart.

assigned to the medical service. At 8:30 the following morning he was given 20 units of insulin and with uncanny precision at exactly two hours after the injection he went into a second coronary attack with symptoms approaching in intensity those of the first. The pain this time, however, remained unabated even after a gram and a half of morphine had been given. An emergency blood sugar taken that same afternoon showed 135 mg. Once more convalescence was prolonged and electrocardiographic stud-

ies (Figure 2) taken seven days later showed increased myocardial damage.

This second harrowing experience definitely precluded surgical interference and discouraged any further insulin administration. The patient now, after a lapse of about six months, is singularly free from cardiovascular symptoms although still maintaining a fairly high blood sugar level of 180 mgs. on a well balanced 1,600 calorie diet.

*Case 2* Y. H., a very obese woman, aged 55, and weighing 238 pounds, was said

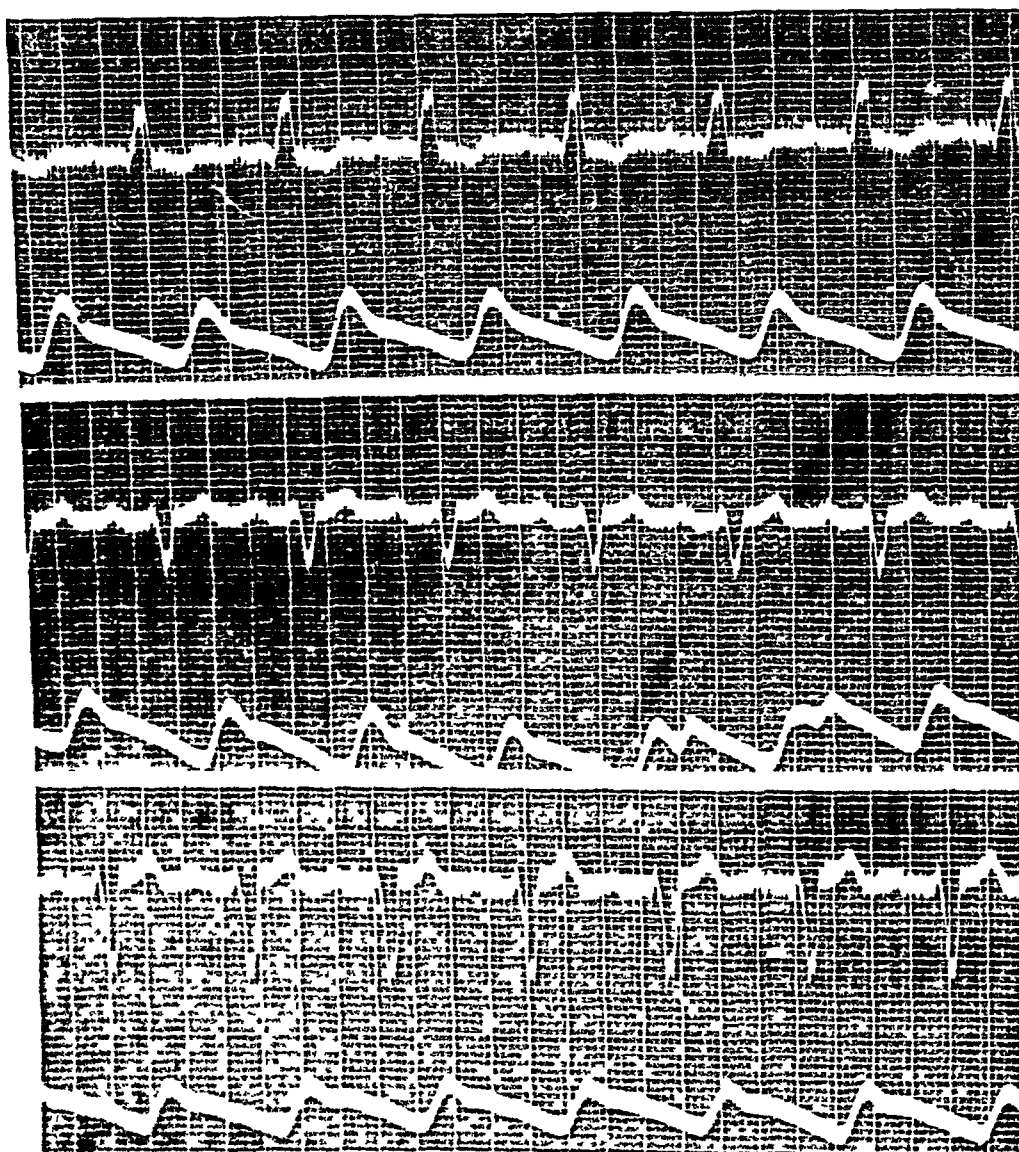


FIG. 2. Graphic records made on November 16, 1928 following a second coronary attack. Note the increased evidence of coronary and myocardial damage. The P-R interval has been prolonged to 0.24 seconds; the QRS complexes are delayed, widened, and split suggesting right bundle branch block. The T-waves are altered in the first lead.

to have had a diabetic history for 21 years. At the age of 34, following child birth, sugar was found in her urine and from time to time in the intervening years the patient was told by her many medical advisers about the large amount of sugar in the urine. With the flagrant and only too common disregard of this type of diabetic who must eat regardless of the consequences, she continually increased both the size of her meals and girth. A progressive dyspnea, even on moderate effort finally brought the patient to the cardiac clinic where careful studies revealed no more than a great overweight

factor. Her blood chemistry, however, showed a hyperphosemia well above 200 and she was immediately transferred to the general medical clinic for treatment. Orthodiagraphic measurements of the heart showed all diameters to be slightly increased while the electrocardiographic studies showed only a moderate left axis deviation (Figure 3). Her blood pressure levels were 140/90.

After a rather futile attempt to properly balance the patient's diet and only to combat a rather troublesome pruritus vulvae which developed recently, insulin was resorted to. For a period of one week, the patient was

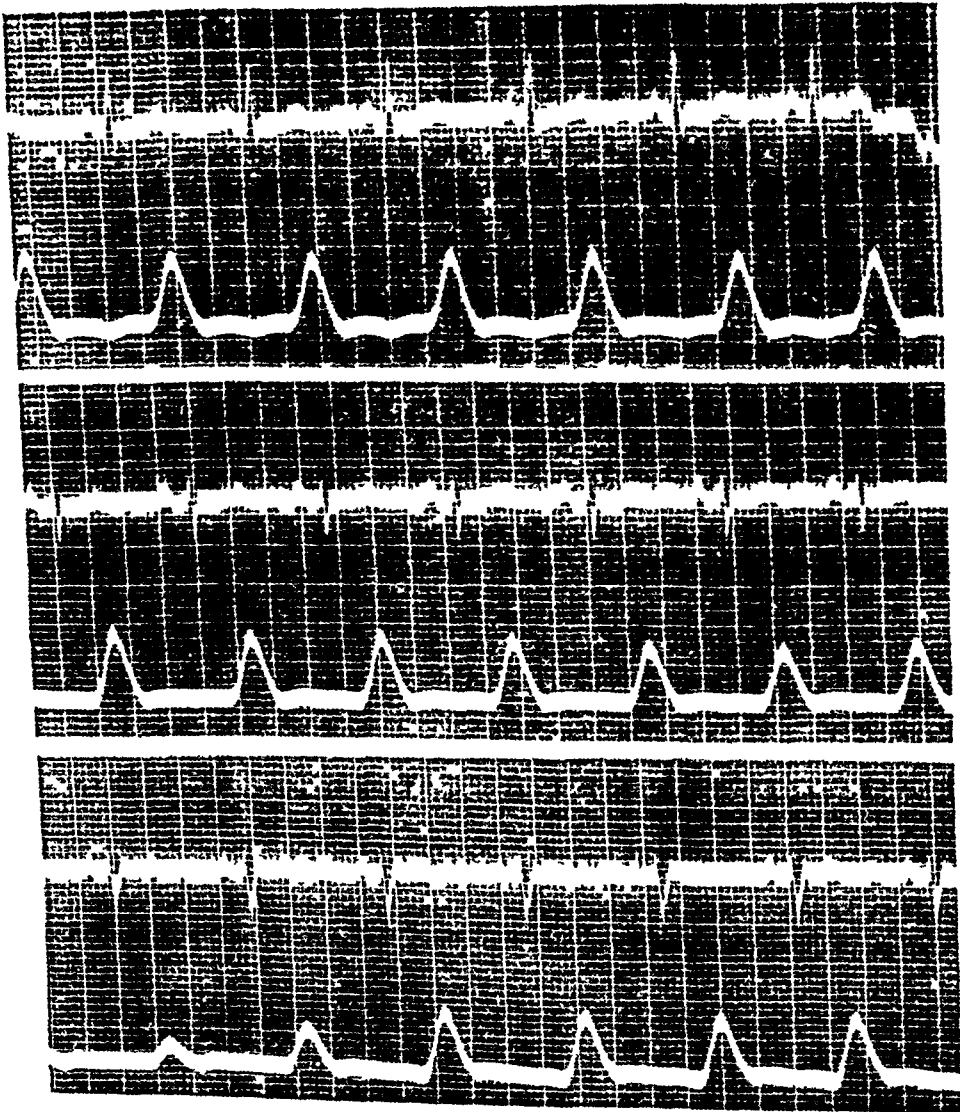


FIG 3 Graphic tracings taken on October 4, 1929. With the exception of a slight left axis deviation, the records are more or less normal for this age period.

given a daily dose of 10 units of insulin during which time the daughter was being instructed in its proper administration. On the eighth day the daughter was told to give the patient 10 units of insulin three times a day.

On the evening of the ninth day, about three hours after the last injection, the patient was suddenly awakened with severe epigastric pain followed by nausea and vomiting. One of our assistants made a prompt diagnosis of acute coronary occlusion. His diagnosis was corroborated weeks later by an electrocardiogram (Figure 4).

disclosing all of the characteristic features of myocardial infarction. In this connection, it is interesting to compare Figures 3 and 4 taken about five weeks apart.

Unfortunately after her convalescence the patient was lost sight of but in our follow-up memorandum of this case it was noted that the patient had again reverted to her previous dietary indiscretions and the memorandum concluded with a note from her daughter saying that while the mother was still suffering from breathlessness and "the itch is just as bad" yet she had had no more

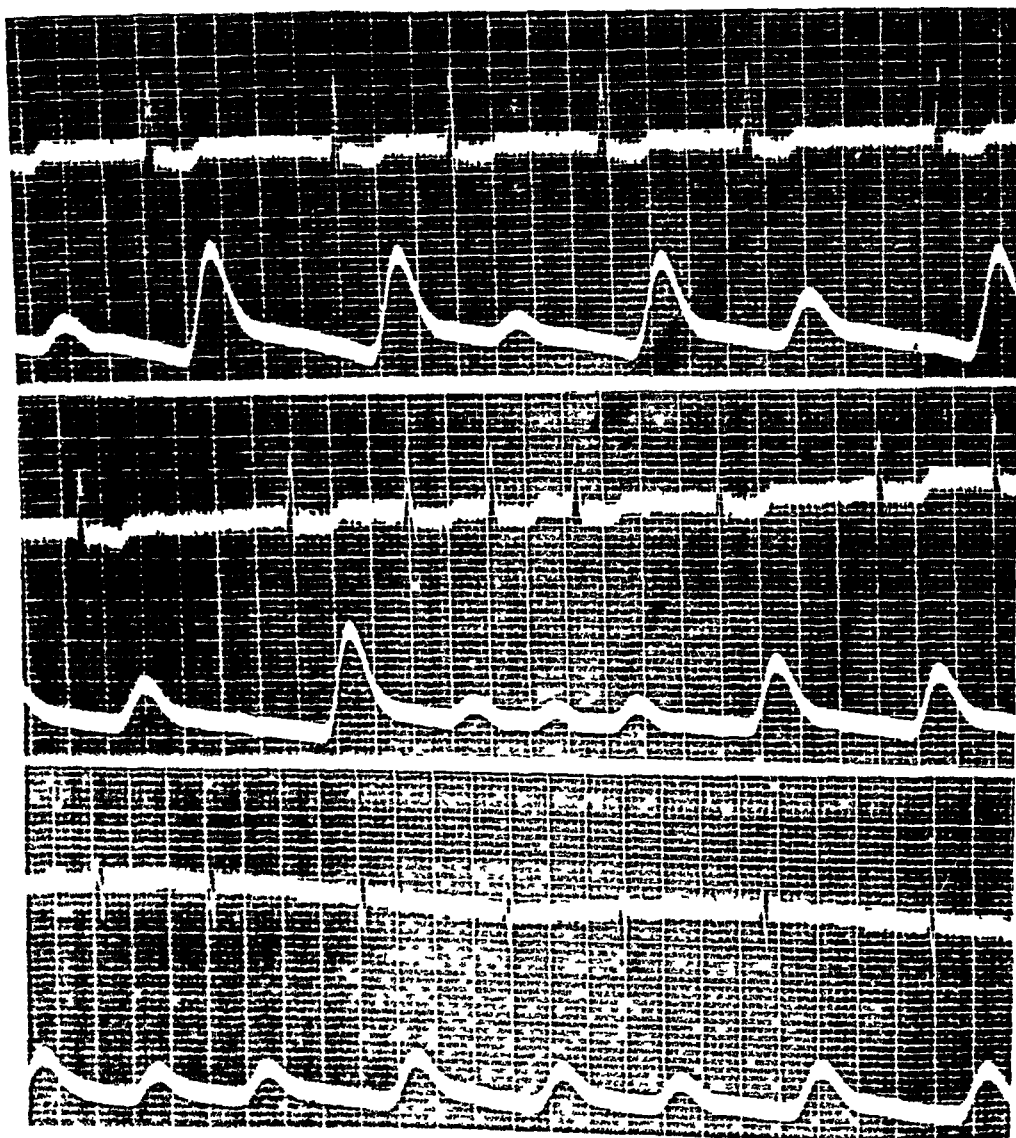


FIG. 4. Records taken on November 9, 1929, about five weeks later. Note the development of auricular fibrillation with T-wave alterations in the first and second leads. The pulse deficit is well indicated in the simultaneous polygraphic tracings.

heart attacks since the injections were stopped

*Case 3* B M, man aged 62, retired manufacturer, known to have had diabetes since 1915 at which time he was being treated for "rheumatic pains" in both lower extremities. For the next nine years he was seen from time to time by many eminent diabetic specialists and sojourned in several of the leading sanatoriums both here and abroad. Careful attention to diet and a routine of restricted activity coupled with carefully systematized exercise permitted the patient to enjoy an uneventful ten years.

Always on the alert for new remedies with the hope of complete cure, the patient soon learned through lay channels of the discovery and development of insulin therapy. On March 8, 1924, after the discovery of a rather high blood chemistry, the patient for the first time was given some insulin—the exact amount of which was not recorded. A few hours later the patient became very nauseated and suffered a severe occipital headache which persisted for almost a week. This first experience with insulin so prejudiced him against the substance that he would not permit its use again until February 10, 1928. At this time, while driving his automobile he apparently suffered a lapse of consciousness as he was subsequently found slumped over the wheel, the front of the automobile having smashed into the rear wall of his warehouse. He was immediately removed to the Hospital where a prompt diagnosis of diabetic coma was made and confirmed by appropriate laboratory tests.

The comatose state continued for 22 hours and only after the liberal use of insulin, glucose and large hypodermoclyses of saline was any appreciable improvement noted.

A new complication had arisen, however, with the return of consciousness he immediately complained of severe pain in the upper chest and unpleasant tingling sensations both in the left arm and leg. This pain persisted in spite of liberal doses of codein and now became the dominant factor in the patient's condition. Up to this time his cardiovascular system had been, with the exception of some cardiac enlargement, essentially negative.

About 24 hours after the onset of the stenocardial pain a definite irregularity was noted in the pulse and the heart sounds, originally of good quality, were supplanted by weak and irregular impulses. The true significance of these symptoms was not recognized until electrocardiographic studies were made and in Figure 5 is shown how much damage the myocardium had undergone in the many years of diabetic pathology.

Convalescence was stormy, uncertain and prolonged, the patient being bed-ridden for nearly five months. He now recalled his previous unfortunate experience with insulin and stubbornly resisted its further use. In view of our experience with other similar cases we were inclined to believe that this patient came within that group of individuals in whom a marked lowering of blood sugar levels would precipitate a coronary attack. With rigorous dietary supervision the patient is still alive but living an exceedingly inactive and cloistered existence.

*Case 4* Mrs J S, age 52, former vaudeville entertainer, had been treated for diabetes for about four years. Her previous medical history was negative except for an attack of malaria which she suffered in New Orleans 18 years previously. Her blood sugar was seldom lower than 175 mgs but at times rose to as high as 240. Her occupation precluded systematic medical supervision as the constant traveling from place to place made the question of proper diet almost an impossible one. The patient was a woman of unusual intelligence and was always aware of the short-comings of her treatment.

On November 18, 1928, during a stay in Cleveland, she contracted a mild influenzal infection which left her rather weak and with a stubbornly persistent bronchial cough. A physician called to attend her upon learning of her diabetic history suggested another blood chemistry. Finding a blood sugar of 280, he became quite alarmed and urged the immediate use of insulin and hospitalization. She refused the latter so that the physician was forced to treat her at her hotel room.

In a resumé of his therapy the doctor stated that he had given her 30 units for an initial dose and followed it about 6 hours later with 20 units more. On the following

day this dosage was again repeated and that evening the patient experienced her first coronary seizure. The symptoms were unmistakable, the dyspneic factor was marked and at one time the onset of pulmonary edema seemed imminent, the pulse rate was very rapid and irregular and the doctor reported that the blood pressure could not be estimated. On the fifth day a very definite pericardial friction rub was heard and the patient made a slow recovery.

She was seen by us in New York about two months later, electrocardiographic stud-

ies made at that time (Figure 6) showed a moderately rapid auricular fibrillation with T-wave alterations in the significant leads. The heart had become markedly enlarged and there was some pretibial edema. The cough was still present, and the sputum was occasionally tinged with blood. This latter finding so alarmed the patient that she had consulted a phthisiologist. In view of her past diabetic history he also suggested insulin and reassured her about the hemoptysis.

Her blood sugar in the meantime still maintained a dangerously high level in spite

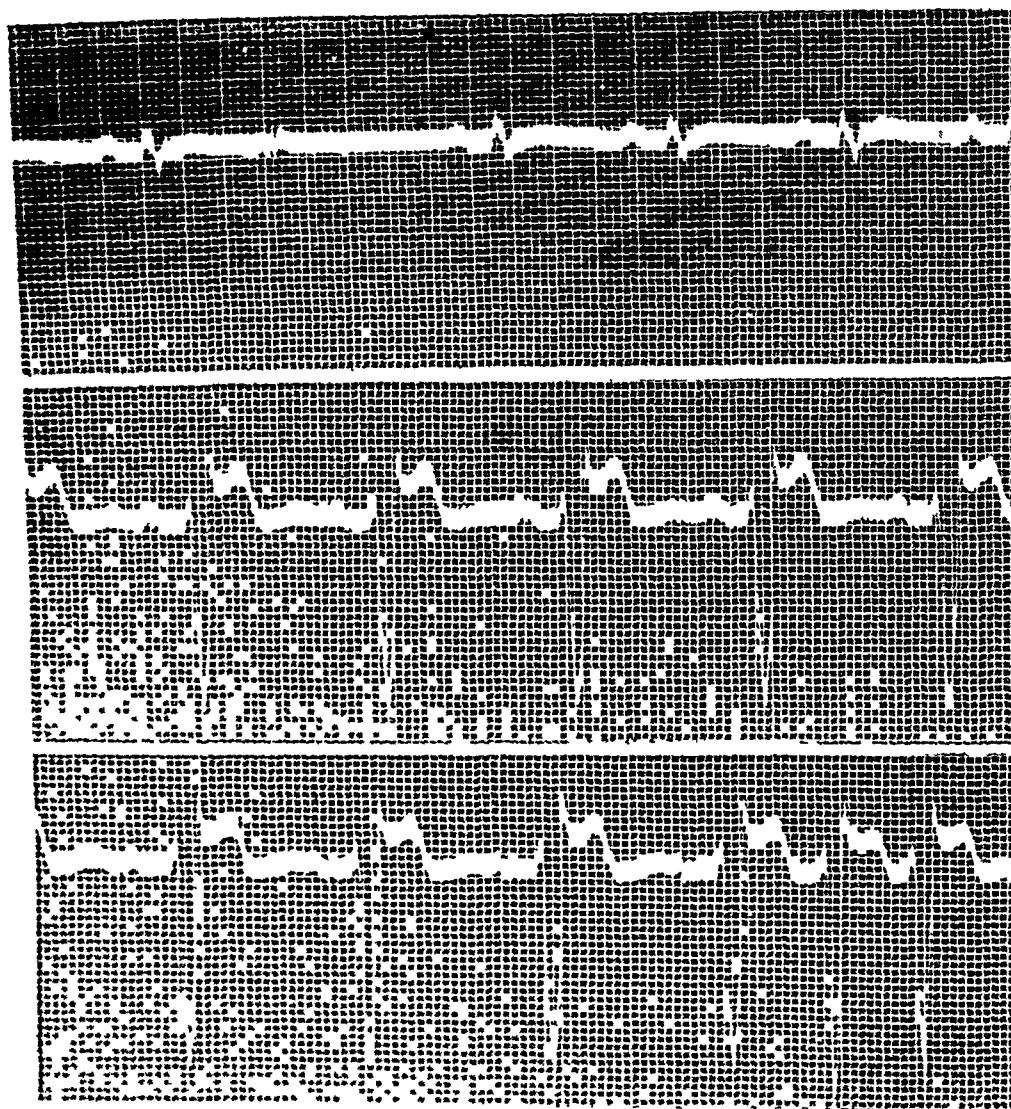


FIG. 5. Electrocardiographic studies made on February 24, 1928, showing extensive myocardial involvement. The P-R interval has been prolonged to 0.22 seconds, the QRS-complexes are widened to 0.12 seconds with a high take-off of the T-wave. In the first lead is shown what apparently is a second degree of heart block with a complete dropping out of the ventricular complex while in the third lead is shown a short run of ventricular extrasystoles. During one such attack of paroxysmal tachycardia, this high rate was maintained for about 40 minutes with extreme prostration on the part of the patient.



of the self-imposed restrictions of diet. She was put on 10 units of insulin three times a day. Five days thereafter she was seized with a severe stenocardial attack and called to her nurse for assistance. She told the nurse that she felt like vomiting and while attempting to get to the bath room she dropped to the floor and expired in a few moments.

The development of stenocardial pain following the administration of insulin is not an entirely new observation, described under a different terminology, many authors have previously pointed out the dangers inherent in the indiscriminate use of insulin, especially in those individuals suffering from arteriosclerosis. Turner for example,

has recently reported such an instance as a phenomenon of insulin shock, his case developed true anginal pain each time subsequent to insulin injection.

In the series of cases reported here, coronary occlusion followed as a result of insulin therapy. Speculations as to the exact physiologic mechanism responsible for these seizures have been based upon the lowered blood sugar levels following the use of insulin. In a heart already impoverished by coronary pathology, the withdrawal of the most important factor in myocardial tissue metabolism unquestionably leads to a further physiologic imbalance. If the current theory of anoxemia is to be given credence heart pain is the



FIG. 6. Electrocardiographic records made on February 2, 1929. Note the rather rapid auricular fibrillation with T-wave changes in the first and second leads. Left ventricular extrasystoles are occurring rather frequently. There is a moderate left axis deviation.



result of lowered nutritional intake on the part of the heart muscle. How much the pain factor is due to insufficient oxygenation or to increased acid concentration of retained metabolic products and how much to insufficient glycogen metabolism is still a nice problem for further laboratory investigation. In spite of the many elaborate researches which have been pursued by many able workers in this field, the present conception of heart pain still revolves around the functional competency of the coronary vessels.

In a heart already adjusted to high sugar levels, partial stenosing of the coronary arterial tree may give no symptoms until a sudden change is brought about by the physiologic action of insulin. It has been pointed out that skeletal muscle does not work more efficiently in the high sugar medium seen in diabetes mellitus, apparently the sugar which circulates in the blood stream of the diabetic individual is unavailable for muscle metabolism until it is altered by the complicated endocrine mechanism controlled by insulin.

Sufficient experimental evidence is at hand to show that the heart muscle gives up its glycogen rather reluctantly but that this exchange is influenced to a highly sensitive degree by many endocrine substances, especially adrenal-in, pituitrin, thyroxin, as well as insulin. From a clinical point of view, however, it is especially important to recognize that these substances, while developing only minor alterations in the normal heart may be productive of widespread change in the cardiac functional mechanism of the diseased one.

Such we believe is the case in those individuals who have had a long dia-

betic history in conjunction with more or less symptomless coronary changes. Where arteriosclerosis is known to be present careful examination of the heart should be routinely undertaken before insulin therapy is started. Electrocardiographic studies may be of the utmost value in determining the selection of cases suitable for insulin treatment. In the cases quoted, coronary arterial disease was unsuspected until the clinical syndrome of occlusion had fully developed, all of these cases suffered coronary seizures but a few hours after insulin administration. It is interesting to note that in none of these cases did the blood sugar levels fall below the so-called margin of safety. For this reason, the attacks cannot be regarded in the light of hypoglycemic shock. While it is true that in this latter condition the symptoms of stenocardia may sometimes be a feature, the prompt response to glucose therapy readily differentiates it from a true coronary attack which is not influenced by such methods.

Although the cases cited suffered attacks of angina pectoris as the result of true coronary disease, there were three other patients in this series who experienced milder stenocardial symptoms without altered electrocardiographic tracings. These three cases responded readily to the nitrates and they may be compared to the case reported by Turner, we have attempted to avoid such borderline cases in this paper.

Where diabetes is complicated by known cardiovascular factors we have studiously avoided insulin therapy until all dietary measures have failed to produce results commensurate with safety.

# A New Modification of Milk for Use in the Dietary Treatment of Peptic Ulcer\*

By RAY C. BLANKINSHIP, M.D. and WM. H. OATWAY, Jr., M.D.,  
Madison, Wisconsin

THE ideal ulcer diet is one which furnishes the fundamental requisites (balanced, with adequate mineral and vitamin content) in a finely divided state and which brings about a minimum digestive effort. When properly modified, and slightly supplemented to overcome the distorted relationship between protein, fat and carbohydrate content, milk and cream can be made to form an excellent basis for such a diet. The pediatricians years ago recognized the importance in infant feeding of a fine soft curd, as well as a balanced diet and slightly acidified milk. Hess and Matzner,<sup>1</sup> in 1924, first recommended the addition of a small quantity of lemon or orange juice to milk fed to infants, but such modification has never been suggested in the dietary treatment of disease in adults. On the contrary, until recently, authors<sup>2, 3</sup> have generally recommended excluding all forms of citrous fruits from the ulcer diet.

Naturally with our increasing knowledge of vitamins physicians everywhere are now using fruit juices quite freely, and, of course, in some instances

where it was formerly thought to be contraindicated. A short time ago Harris<sup>4</sup> included both orange and tomato juice in his ulcer diet, saying that they have been shown to bring about no increase in gastric acidity. Similarly Cowdhas<sup>5</sup> has used orange juice while discussing vitamin B deficiency as a possible causative factor in ulcer. We believe we are the first to use milk modified by the addition of large quantities of orange juice in the dietary treatment of peptic ulcer, and to define all the principles involved, at the same time reporting the practical application in the actual treatment of patients.

It is noteworthy that the carbohydrate in orange juice (1 gram to 10 ccs) has been shown to inhibit hunger contractions of the stomach.<sup>6</sup> It is also known to leave the stomach very rapidly,<sup>7</sup> and it is a readily available source of metabolic energy bringing about a minimum amount of gastric secretion and it does not cause pain.<sup>8</sup> The addition of orange juice to milk permits the feeding of more juice than might otherwise conveniently be given. This is not undesirable because additional carbohydrate is needed to aid in balancing the diet. The large quantity of juice used obviously increases the vitamin content and adds a mild laxa-

\*From the Department of Medicine, State of Wisconsin General Hospital, Madison, Wisconsin.

tive effect The incidental factor of dilution is certainly beneficial rather than harmful

Our work includes a study of milk and cream mixture with orange juice, sodium citrate, citric acid and tomato juice, in the proportions indicated These mixtures were examined in vitro and then fed to subjects known to

have uncomplicated duodenal ulcer All patients used were in the second week of therapy, with rest and citiated milk the two main factors in previous treatment The formulas used in each case, with intervals between feedings and aspirations, are given below In each case the large Ewald stomach tube was easily passed and the stomach emptied

#### FORMULAE OF MIXTURES AS FED TO PATIENTS

3-11-30	Milk and Orange Juice
	8 ounce feeding of a mixture of milk 24 ounces, cream 8 ounces and orange juice 10 ounces
	This was aspirated 45 minutes after feeding
3-13-30	8 ounce feeding of a mixture of milk 12 ounces cream 4 ounces and sodium citrate 8 gms
	Aspiration 45 minutes after the feeding
3-18-30	Milk and citric acid
	8 ounce feeding of a mixture of milk 12 ounces, cream 4 ounces and citric acid 1½ grams
	Aspiration 45 minutes after the feeding
3-18-30	Milk and tomato juice
	8 ounce feeding of a mixture of milk 12 ounces, cream 4 ounces, tomato juice 2 ounces
	Aspiration 45 minutes after the feeding

The stomach contents were examined for free acid, a pH determination was made in every case, the curds were examined and photographed (See Chart I, figures 1 to 7, magnification of photographs 27 diameters)

CHART I  
DATA FROM GASTRIC ANALYSES

Name	Mixture	pH <sup>1</sup>	Free HCl	Photograph	Description
Mr T }	Orange	1.71	18	Figures	Very finely
Mr H }	Juice			1 & 2	divided curd
Mr T }	and Milk	1.35	42'		formation
Mr H }	Sodium	3.33	0	Figure 3	Fairly fine
Mr T }	Citrate				curd in
Mr H }	and Milk	3.10	0	Figure 4	mucus
Mr T }	Citric	1.50	8	Figure 5	Moderate size
Mr H }	Acid				curds (larg-
	and Milk	1.67	18	Figure 6	est curds
					photographed)
Mr J	Tomato				Very coarse
	Juice	1.05	0	Figure 7	curds, grossly
	and Milk				and micro-
					scopically

<sup>1</sup>pH determinations made by the potentiometric method

<sup>2</sup>Previous meal partly retained



FIG 1



FIG 2

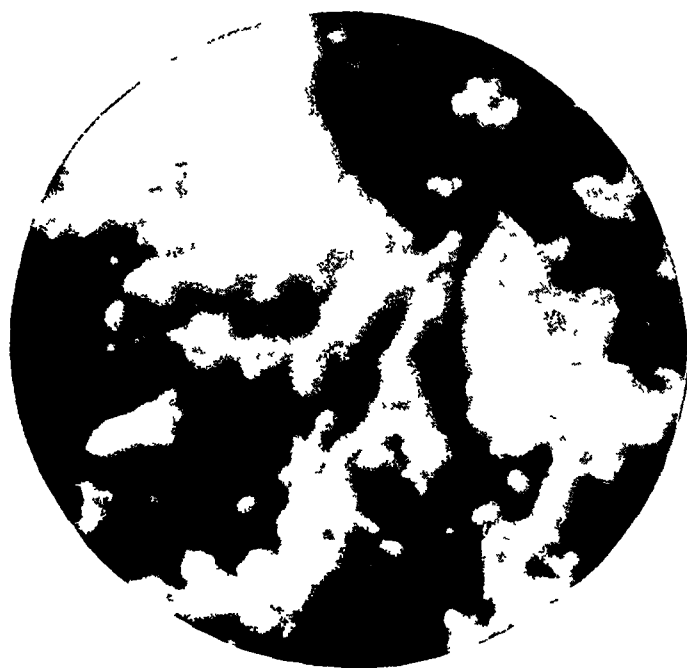


FIG 3



FIG 4

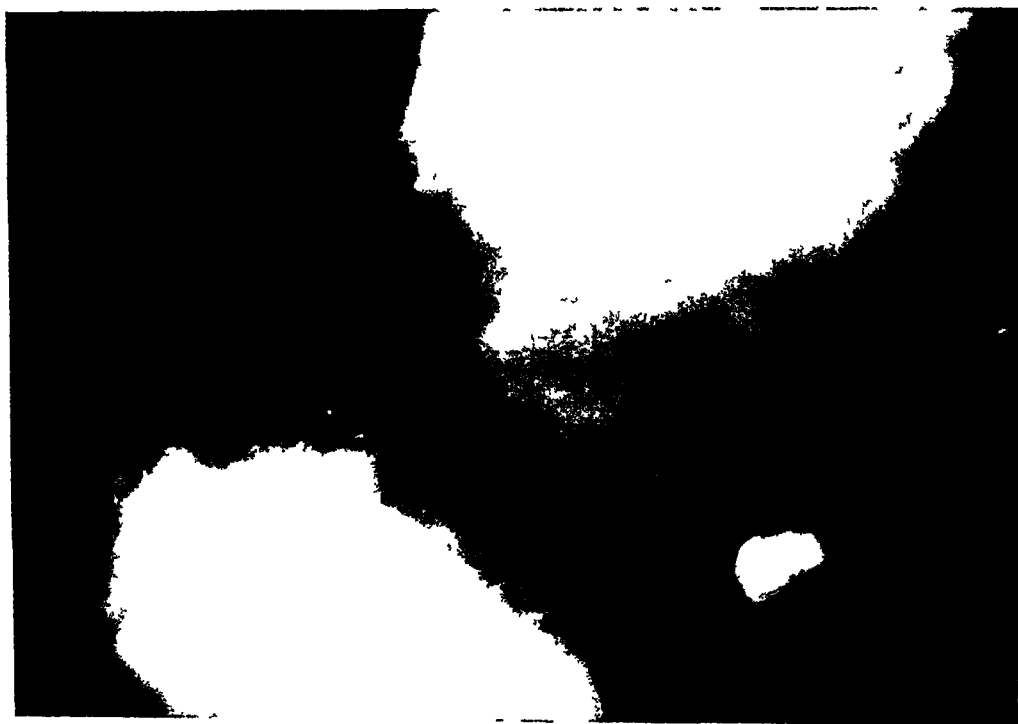


FIG 5

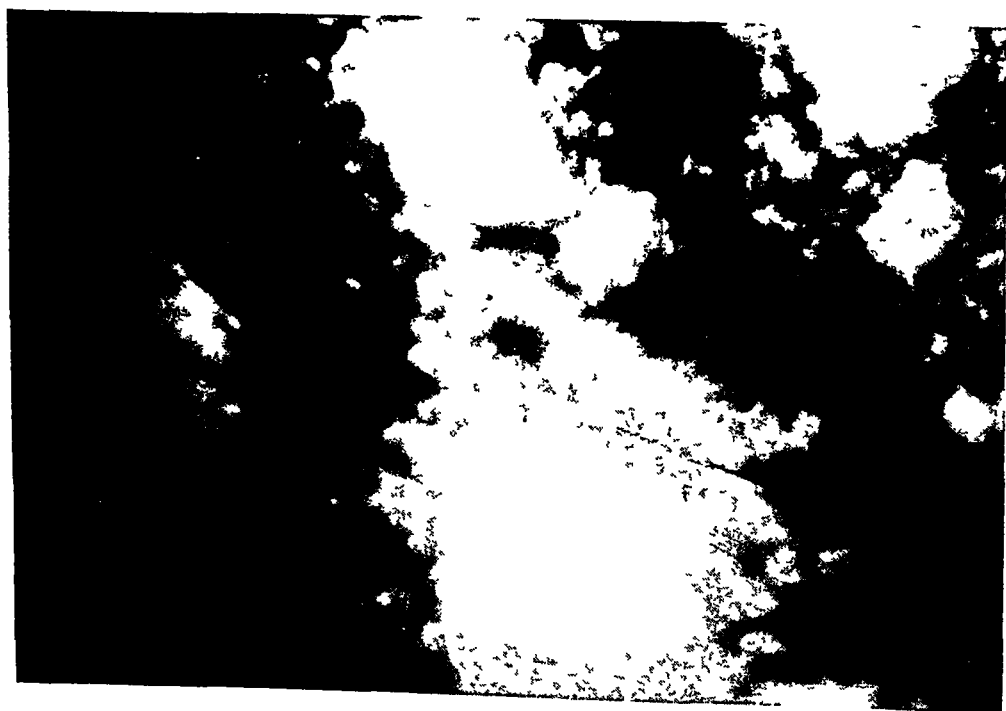


FIG 6

From gross examination and photograph of the curves we are able to make the following deductions

- 1 The orange juice mixture produced the softest and finest curds Dilution, of course, might have some influence in this observation
- 2 Sodium citrate curds are relatively fine though tougher and somewhat enmeshed in mucus
- 3 The citric acid curds were relatively larger, but soft and more evenly distributed
- 4 Tomato juice may be excluded entirely from consideration, because of its disagreeable taste and the large tough curd formation

Since our initial aim in this work was to acidify milk with orange juice to a point equal to that of ordinary citric acid milk (four grams to the

liter) as usually fed to infants,<sup>9</sup> we have plotted curves showing the pH values of milk when an increasing amount of orange juice is added to a constant volume of milk (75 ccs) For comparison similar curves are charted for N/10 hydrochloric acid and three per cent citric acid (See Chart II) Note that three varieties of oranges were used and that the pH values of these undiluted juices are shown We did not try to feed milk having the same pH as that of citric acid milk because to do this would bring about immediate curdling and render the mixture less palatable than that recommended (See Chart II, Diet 34) This mixture as used is approximately 25 per cent orange juice and just falls short of curdling before ingestion It is highly palatable and by most patients is preferred to the other commonly used modifications

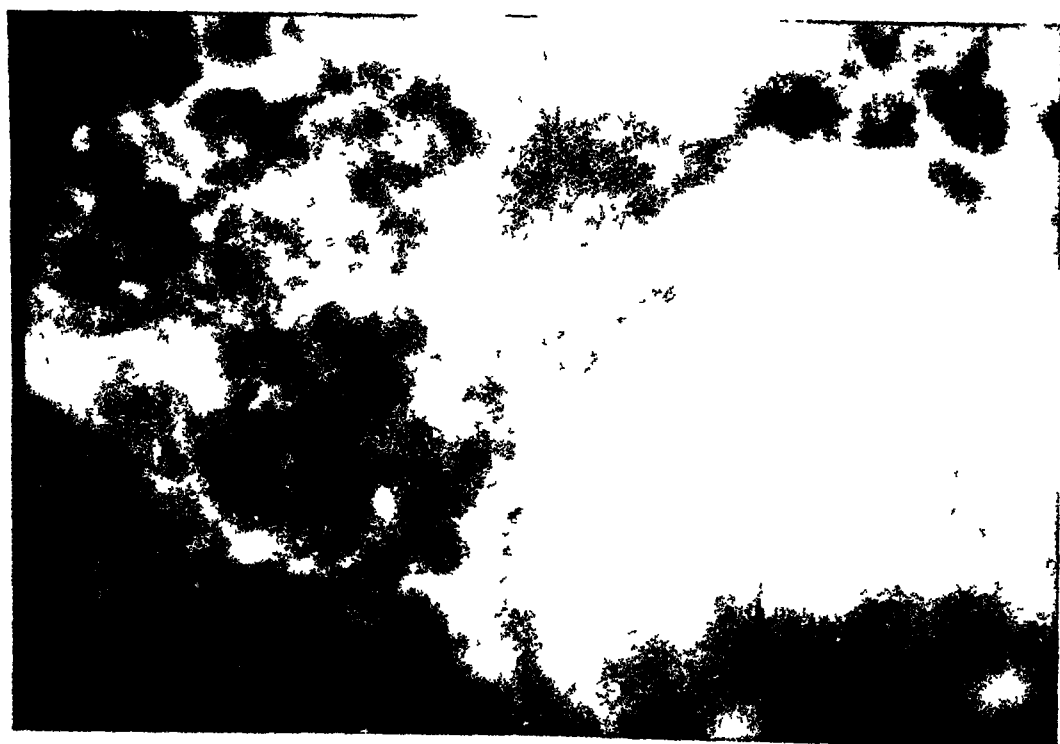


Fig. 5

For the past six months, during the initial period of dietary treatment of peptic ulcer, while the patient is still at rest in bed, we have used the formula below with highly satisfactory results

up the caloric value where it is most needed (carbohydrate) and does not materially alter the taste. The cost of the suggested mixture has been shown to be normally no greater than the old half milk and half cream diet. Ad-

Milk	Ounces—24
Cream	" — 8
Strained orange juice	" — 10
Sugar	Grams—20
Total Protein 32, Fat 77, Carbohydrate 96	
Calories 1205	

This is given in six ounce feedings every two hours, from 8 A M to 8 P M. The addition of sugar brings

conditions can be made to this diet according to well recognized principles recently restated by one of us<sup>10</sup>

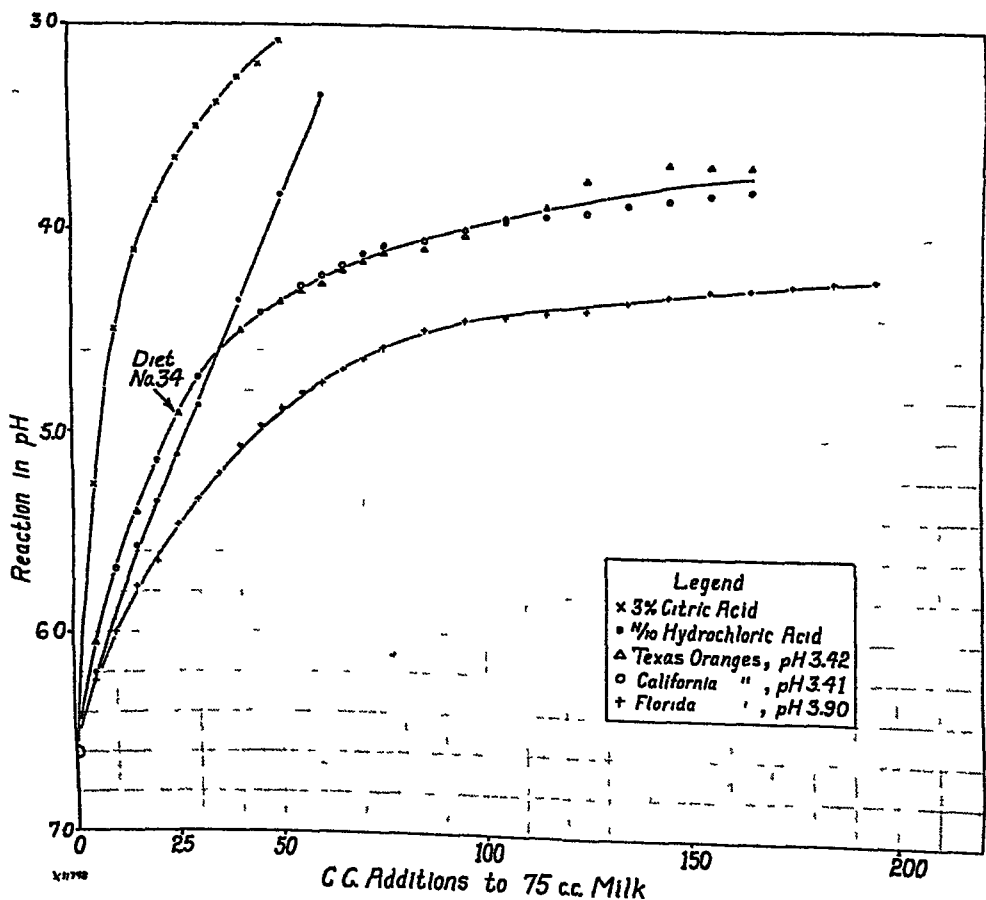


CHART 2



## CONCLUSIONS

- 1 A new ulcer diet using milk modified by the addition of orange juice is suggested and a definite formula outlined for its use in the early treatment. The diet is appropriately balanced and meets the demands made by the ulcer bearing stomach.
- 2 A diagram is attached showing the pH value of California, Texas and Florida oranges undiluted and when these juices are added to milk in increasing quantity range from 0 to 70% fruit juice. Similar curves for comparison are charted for N/10 hydrochloric acid and 3% citric acid.
- 3 Photographs show the curd formation in the aspirated stomach contents in ulcer patients. After feeding (a) milk, cream and orange juice mixture, (b) citric acid milk, (c) milk citrated by the addition of sodium citrate, and (d) milk plus tomato juice.

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# A Clinical Study of Duodenitis, Gastritis and Gastrojejunitis\*

By ANDREW B. RIVERS, M.D., *Division of Medicine, Mayo Clinic,  
Rochester, Minnesota*

IN a statistical study of 2,000 necropsies, Robertson and Hargis were able to demonstrate scars or ulcers in the stomach or duodenum in almost 20 per cent

Various hypotheses have been advanced to account for the origin of peptic ulcer and the successive pathologic steps through which a lesion passes before it finally results in chronic ulcer. Because of the radical surgical measures for the cure of ulcer instituted under certain schools, much additional material for study is being collected. Instead of the problem being clarified, it is becoming more complex. Lesions of every degree of severity, ranging from a simple superficial inflammatory spot on the mucosa to chronic perforating ulcers passing through all the coats of the viscus are frequently demonstrable in the same stomach or duodenum.

In this paper I shall consider briefly some of the lesions which are almost universally considered to represent the original or the intermediate stages in the development of ulcer. The material

for study includes 191 surgically verified cases of duodenitis, gastritis and gastrojejunitis of which I am reporting ten illustrative cases.

Aschoff, in discussing the relation of mucosal erosions to the development of ulcer of the stomach, intimates that the cause of the erosion is not necessarily the cause of the ulcer. He stated "This division of the problem into two parts seems to me to be the more justifiable, since with the eventually different genesis of erosion and of ulcers we must proceed in a different fashion prophylactically and therapeutically. Thus it might be conceivable that although we were unable to prevent the genesis of erosions, we might learn to avert their transformation into true ulcers. Naturally it should also be our endeavor to prevent the genesis of erosions since it is indeed from these that ulcers first develop."

Aschoff divided erosions into two types: erosions in the fundus, which are superficial and heal readily, and erosions of the gastric pathway, which he believes to be the precursors of ulcer. He continued "In fundus erosions venous stasis and the spasmodic motions of vomiting play a particular part. In the erosions of the gastric pathway it is apparently pe-

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\*Abridgment of thesis submitted to the Faculty of the Graduate School of the University of Minnesota in partial fulfillment of the requirements for the degree of Master of Science in Medicine, 1929.

cular spastic conditions of the pathway itself or arterial blockings, whether of a spastic, embolic or arteriosclerotic nature, that call forth the necrosis of the mucosa "

During the last few years much renewed interest is being shown in the localized or diffuse inflammatory lesions involving the stomach and duodenum. MacCarty reviewed ninety-two pathologic specimens of inflammatory lesions in the duodenum (duodenitis). In such specimens he invariably found cellular destruction, with congestion, edema, and migration of polymorphonuclear leukocytes, lymphocytes and endothelial leukocytes. These lesions, when localized, present serosal changes indistinguishable from small ulcers, but when they are diffuse the appearance of the organ is different from that when the changes are produced by ulcer. Judd described an ulcer that is of the type of duodenitis. He distinguished this from the usual duodenal ulcer by the absence of a distinct crater.

Konjetzny found that in a series of gastric and duodenal ulcers which he studied there was more or less extensive gastritis and duodenitis. Certain authors have recently refuted the claim that there is a high incidence of gastritis associated with gastric lesions. According to Konjetzny chronic ulcer develops on the base of chronic duodenitis as the result of unknown functional mechanical factors.

The acute or chronic shallow lesions of the stomach and duodenum such as mucosal erosions and lesions of localized or diffuse gastritis and of duodenitis have been recognized as pathologic entities for many years. In recent years, since gastro-enterostomy has become

such a common procedure in the surgical treatment of ulcer, opportunities have been afforded from time to time for the study of acute shallow lesions around the anastomotic opening. These present the usual pathologic pictures seen in acute duodenitis or gastritis. Sometimes, the lesions present superficial localized inflammatory areas, again, hemorrhagic patches around the anastomotic opening are distinguishable. Occasionally these extend down into the jejunum, at other times, shallow erosions can be seen scattered around the stoma.

It seems to me that the significance of these shallow gastroduodenal lesions has been underestimated. Occasionally certain writers report that they are a possible source of hemorrhage but it is assumed that they heal quickly and thus they are usually considered of little clinical significance. Others consider them merely the intermediate stages through which a lesion must pass to become a chronic ulcer.

It may be true, as Konjetzny suggested, that duodenitis is the forerunner of chronic duodenal ulcer, but it is by no means true that duodenitis always goes on to ulceration.

The resulting lesions do not always heal rapidly nor must they develop into chronic peptic ulcers before they become significant clinical entities with definite symptoms. Recently I reported cases in which the salient complaint was of massive gastro-intestinal hemorrhages. At operation, acute nonulcerating inflammatory areas in the stomach or duodenum or around the gastro-enteric stoma were found. In all these cases, there was definite evidence of focal infection. Material from infected

dental roots in these cases, when injected intravenously, produced in all instances acute hemorrhagic gastroduodenal lesions in experimental animals. The lesions commonly observed in these animals were of three types.

Ulcers of the first type were shallow and single, or multiple. They were scattered about the first portion of the duodenum, or over the pyloric portion of the stomach. There was loss of mucosa, sometimes also of submucosa, but as a rule the ulcerating process left the muscularis intact. Occasionally the ulcers perforated all coats of the viscus, and produced rapidly fatal peritonitis.

The second type of lesion, and the one which probably was most frequently seen may be described as a series of pin-point hemorrhagic submucosal stipplings. These occurred anywhere in the stomach or duodenum, but most frequently were found in the duodenum running in a line parallel to the fibers of the pyloric muscle in the area usually selected as the site of duodenal ulcer.

The third type of lesion was similar to the second, but instead of separate stippled zones there were one or more large submucosal hemorrhagic areas which ranged from 1.6 to 4 cm in diameter.

It is possible that all these lesions are merely different stages of the same process, observed at varying stages in their development.

#### DUODENITIS

This part of the study includes 157 cases of surgically verified ulcerating and nonulcerating duodenitis of which seventy-four were cases of duodenitis without ulcers. In most of these cases sections were removed and the diag-

nosis was confirmed by microscopic examination.

From the analysis of the histories of cases, I am inclined to believe that the small, shallow, inflammatory lesions involving the duodenum can be productive of symptoms quite as serious as are those caused by definite ulceration. The specimens removed in these cases presented reactions of extreme variability, ranging from slight areas of hyperemia to extensive inflammatory changes involving the entire duodenal wall and including, at times, extensive ulceration. Nagel, in discussing this type of lesion stated "In a microscopic section of the affected area all the changes found in subacute and chronic inflammatory processes are seen. The epithelium is generally intact but may be denuded in a few small areas and epithelial cells are seen in various stages of degeneration. Where the epithelium is absent the surface is covered by fibrinous exudate rich in lymphocytes, plasma cells and occasional eosinophils. In areas in which inflammation is more acute a fair sprinkling of polymorphonuclear leukocytes is found. In most instances the mucosa and submucosa are involved and occasionally the cellular infiltration extends through the muscle layers to the serosa. There may be a perceptible increase in fibrous tissue especially in the submucosa. The vessels of the submucosa also show some engorgement but this is most marked in the serosa which is generally congested and thickened."

*Case 1* Nonulcerating areal duodenitis. A man, aged thirty-seven years, entered the clinic complaining of epigastric pain. About one year prior to admission a severe gastric hemorrhage had occurred suddenly. Pre-

monitory symptoms and untoward effects had not occurred. He apparently had been in good health until four months prior to admission, when a second hemorrhage had occurred. Two months prior to admission, epigastric discomfort had begun, this had appeared fifteen or twenty minutes following meals and had been a daily occurrence since the time of its appearance as a symptom. There had been much belching and a feeling of distention high in the epigastrium. Pain never had been severe but it frequently had radiated from the epigastrium through to the back. Roentgenographic examination showed evidence of deformity of the duodenum which lacked the usual characteristics of ulcer. Titration of gastric contents gave values of 74 for total acidity and 58 for free hydrochloric acid in terms of tenth-normal sodium hydroxide. Exploration revealed a superficial inflammatory area in the wall of the duodenum immediately distal to the pylorus, with definite thickening and inflammation in the gastrohepatic omentum. The appendix was found to be chronically inflamed.

*Case 2. Duodenitis with shallow ulcer.* A woman, aged thirty-eight years, for twelve years had had intervals during which, for two to three days she had suffered from distress in the upper part of the abdomen. Pain had come on shortly after meals. Fats and fried foods had seemed especially to cause trouble. The pain usually had been in the mid-epigastrium, radiating from there to the back. For the period shortly before she had come to the clinic, the pain had come on at more regular intervals, usually about 4 p. m. and again at 11 p. m. Soda had been found to give prompt relief of symptoms. The total acidity was 76 and the free hydrochloric acid was 58. Duodenal deformity was noted on roentgenographic examination. There was definite dental sepsis. At operation diffuse duodenitis was found with a small ulcerated area 6 mm. in diameter.

*Case 3. Duodenitis with subserosal scar.* A man, aged fifty-nine years, for about twenty years several times each year had had attacks of trouble referable to the stomach. This usually had come on in the

spring and autumn. For several weeks at that time he had had trouble daily. He described his symptoms as a sensation of fullness and heaviness as well as of some soreness in the epigastrium one or two hours after meals. Soda had been found to give prompt relief. During the two years preceding consultation at the clinic he had had daily distress similar to that described. Soda still had relieved the distress. He never had had any real pain. Total gastric acidity was 74 and free hydrochloric acid was 56. The roentgenographic examination revealed evidence of duodenal deformity. At operation chronic duodenitis, with subserosal scar and congestion, was found.

*Comment on duodenitis.*—This series includes eighty-two cases of duodenal ulcer with duodenitis and seventy-five cases of nonulcerating duodenitis.

In 1926, Nagel carefully reviewed the clinical histories and pathologic data in twenty-six cases of duodenitis. Fourteen of the patients were women and twelve were men. In this series of 157 cases the ratio of males to females again assumed proportions more closely simulating those seen in duodenal ulcer. Of the patients who had both duodenitis and ulcer, fifty-nine were men and twenty-three were women, of those who had duodenitis without ulceration, fifty-six were men and nineteen were women. The ages of the patients included in this group varied from twenty-two to seventy-four years, the average age of patients with areas of nonulcerating duodenitis was forty years and with ulcerating duodenitis, forty-two years. The longest period of symptoms was fifty years and the shortest one week. The average duration of symptoms was nine years in those patients who had duodenal ulcer and duodenitis whereas the patients with duodenitis alone experienced

symptoms for an average period of a little less than eight years. This latter fact seems of obvious significance. Some observers are of the opinion that duodenitis is a precursor of ulcer and is a lesion which becomes of clinical significance only when ulcer has developed. It is obvious, however, that a formidable group of symptoms can be caused by duodenitis in association with which there is no evidence of ulceration. Duodenitis with ulceration, like duodenal ulcer, seems to be found more frequently in the nervous, high-strung, apprehensive type of person. Eighty-five per cent of these patients were engaged in trades or professions requiring mental rather than physical exercise.

From the histories of the cases which I reviewed, I was unable to formulate a syndrome sufficiently definite to be characteristic of duodenitis. Analysis of cases in which both ulcer and duodenitis are present usually reveals a syndrome that is definitely characteristic of ulcer. In 54 per cent of the cases, the history included the symptoms usually accepted as being due to peptic ulcer; in an additional 26 per cent the symptoms, although presenting some irregularities, still maintained characteristics suggesting peptic ulcer. In 20 per cent, however, it would have been impossible to arrive at a diagnosis of a duodenal lesion, if the roentgenologist had not visualized irregularity of the duodenal bulb. In those cases in which ulceration was not associated with the duodenitis, the history was indefinite. In 37 per cent the usual characteristics of ulcer were present, in 33 per cent a few symptoms suggested ulcer, and in 30 per cent the

history did not present any of the symptoms usually found with ulcer.

In duodenitis with ulcer, the sequence of pain, food, ease is fairly consistently maintained. The pain is frequently described as a dull, deep-seated soreness not infrequently referred from the epigastrium to the back. I have suggested previously that pain in the back in patients with ulcer argues for a penetrating lesion. Analogous to this is the pain in the back or in the chest as one of the symptoms of nonulcerating duodenitis. These lesions, although not complicated by ulceration, frequently are found to involve intensively the muscularis and serosa as well as the periduodenal tissues. The pain is likely to be less definitely localized to a small area in the epigastrium than in cases of uncomplicated peptic ulcer, and often the area of which maximal complaint is made is not designated as epigastric in situation but rather as diffusely distributed through the entire upper right abdominal quadrant. This pertains particularly to the cases in which there is duodenitis without ulcer. The pain may have a definite qualitative relationship to the taking of food, fatty and fried foods are particularly troublesome. The distress, even though attributed by patients to certain foods, usually reaches maximal severity from one to three hours after the meal. Food and soda, although not as consistently efficacious in relieving symptoms as in cases of simple ulcer, nevertheless are often employed by these patients to obtain some relief.

In about 20 per cent of the patients who had duodenitis only, the complaint was not of pain but of nausea and a

distressing sensation of fullness in the upper right part of the abdomen. Although this sensation might come on shortly after meals, it usually reached maximal intensity several hours after ingestion of food. The patients resorted to alkalis more frequently than to food in order to obtain relief from symptoms.

Jaundice occasionally occurred, although at operation pathologic change in the gallbladder was not demonstrable. In such instances, the jaundice was probably the result of the extension of the inflammatory process to the ampulla or from an associated infectious process in and along the biliary ducts.

Although in a few cases of nonulcerating duodenal lesions, there was evidence of temporary retention, definite pyloric obstruction was not found. The retention was caused, no doubt, by reflex pylorospasm.

Hemorrhage is not a rare complication in these lesions, it occurred in 15 per cent of the total number of cases included in the series. Further evidence that inflammatory, nonulcerating duodenal lesions are entities of intrinsic importance is adduced by the fact that gross hemorrhages occurred in 12 per cent of these cases. In some instances, bleeding was the first and only symptom of duodenitis. I have had patients under observation who have had repeated hemorrhages and a vague type of dyspepsia which did not present any of the symptoms usually attributable to ulcer, and at operation only a small patch of duodenitis was found. Hemorrhages may occur by mouth or by bowel. At times the hemorrhage

amounts to oozing only, and at other times it is very extensive.

Kirklin recently reviewed the roentgenologic data in a series of cases of duodenitis. He noted certain differences, roentgenologically, between duodenitis and frank duodenal ulcer. The most significant of his observations appears to be the following: "As a rule the bulb is quite irritable, greatly deformed and diminished in size, often it is represented by a mere skeleton of barium content. Margins of the bulbar shadow tend to be hazy and indistinct. Apparently the bulb is highly irritable, characterized by writhing, rapid emptying, making it very difficult to fill the bulb for any length of time, and the spastic deformity is not only more pronounced than that produced by a true ulcer but it is also more unstable. To this rule there are occasional exceptions, the contour of the distorted bulb being immobile and sharply defined. Since a crater is lacking, no marginal niche or central barium fleck can be seen. By manipulation the examiner may transitorily pen up a bit of barium in a spastic recess and mistake the latter for a niche, but its inconstancy should put him on guard."

#### GASTRITIS

Gastritis as an entity of clinical and pathologic significance has been widely discussed during recent years. The widespread use of "dyspepsia" and "gastritis", as synonymous terms, has led to the careless diagnosis of "gastritis" in the presence of too many ill-defined syndromes involving complaints of distress in the upper part of the abdomen. The misuse of the term gastritis has aroused some hesitancy in accepting this as an unquestioned

diagnosis in cases in which there is a prolonged history of dyspepsia

Most gastro-enterologists admit the existence of acute and of chronic gastritis, but it is doubtful whether any diagnosis is more frequently used as a subterfuge for indecision regarding the complaints of the dyspeptic patient. Consequently the diagnosis of gastritis is infrequently made by careful gastro-enterologists except, perhaps, in those cases in which food poisoning or chemical irritation has produced acute gastro-intestinal symptoms

This paper is not intended as a disquisition on a subject which obviously needs much systematic investigation and clarification, its object is merely to focus attention on it again by presenting instances in which gastro-intestinal symptoms were found at laparotomy to have been due to non-ulcerating inflammatory gastric lesions

There seems to be no doubt that localized, or even more diffuse, areas of gastritis can be productive of syndromes of definite clinical significance. Lesions varying from small, localized, inflammatory spots on the mucosa to extensive pathologic processes involving large areas, are frequently observed. These are occasionally found associated with gastric, duodenal or gastrojejunal ulcers, or even with carcinoma. At times definite syndromes, including the symptom of hemorrhage, may be found, on the operating table, to be attributable to a small, localized area of gastritis. When excised, the result may be complete cessation of the symptoms for which relief was sought. The recent work of Faber is of considerable interest. He stated "We realize, then, that the very oldest

hypothesis, advanced by Cruveilhier, is once more coming in the front, that it is in the gastritis we must seek the origin of the chronic ulcer, and that the frequent ulcerative pyloric gastritis is the cause of the gastropyloric ulcers. Gastritis is likely to assume that predominant position in lesions of the stomach which has been assigned to it from time to time in the past, only to be subordinated to the theory of nervous functional disturbance and chronic simple ulcer"

*Case 4* Nonulcerating areal gastritis with hemorrhage. A woman, aged thirty-two years, had complained of nervousness all her life. She stated that, as a child, she had been afraid of everything. For ten years before she had come to the clinic she had been especially excitable. There had been periodic spells of vomiting, which had been preceded by some nausea, but there had been no pain. The vomiting had not been of the retention type. Three years before admission, without any preliminary gastric disturbance, she had vomited blood. Thereafter, vomiting usually had occurred two or three hours after meals, and usually had been preceded by a brief period of nausea as well as by a sensation of heaviness in the abdomen. The symptoms had been definitely related to certain types of food, cauliflower, cabbage, fried food and bananas had caused moderate gastric pain. General examination gave practically negative results except for tenderness in the region of the gallbladder. Total gastric acidity was estimated at 14, free hydrochloric acid was absent. Roentgenograms showed evidence of a lesion at the outlet of the stomach. The Wassermann reaction was negative. Exploration revealed an area of localized gastritis, about 3 cm in diameter, just above the pylorus. A section was removed for diagnosis and was found to consist of inflammatory tissue.

*Case 5* Uncomplicated nonulcerating gastritis. A man, aged thirty-two years, came to the clinic stating that ten days prior



to his visit he had been awakened by severe pain in the epigastrium. The pain had been referred upward into the chest. He had felt very much nauseated and had vomited several times. His condition had gradually improved, and on a regimen of milk and alkali he had been comfortable. On general examination, rather marked tenderness over the epigastrium was disclosed. The patient was pale. Values for total gastric acidity ranged between 12 and 8. There was persistent absence of free hydrochloric acid. Roentgenologic examination gave evidence of a perforated ulcer at the pylorus. Hemoglobin was estimated at 48 per cent, the number of erythrocytes was 2,620,000, and of leukocytes, 5,700 in each cubic millimeter. At operation, a region of diffuse thickening was found in the wall of the stomach near the pylorus. This was resected and microscopic investigation showed evidence of gastritis and moderate edema of the walls. Ulcer or carcinoma was not found.

*Case 6* Shallow gastric ulcer with atypical gastritis. A man, aged thirty-nine years, had a history of dyspepsia that dated back thirteen years. There was a complaint of pain in the epigastrium that came on one to two hours after meals. Food and soda had relieved the distress promptly. Occasionally the patient had been awakened at night by pain. Two weeks prior to examination he had had severe mid-epigastric pain which had been referred through to the back. Fatty, greasy food always had caused much belching and bloating and a feeling of distress in the stomach. Examination revealed nothing of significance. Analysis of gastric content showed total acidity of 76 and free hydrochloric acid of 64. Roentgenologic examination revealed the presence of a perforating ulcer high on the lesser curvature of the stomach, and a duodenal ulcer. A chronic, perforating gastric ulcer 18 mm long by 12 mm wide was found, also shallow ulceration 5 mm in diameter, accompanied by diffuse gastritis was present. There was also an ulcer in the duodenum.

*Case 7* Interstitial gastritis. A woman, aged fifty-eight years, at the age of fifty-six years had begun having distress in the upper right abdominal quadrant. This distress had

been characterized by a dull, aching type of pain associated with tenderness to the right of and slightly above the umbilicus. She had had a rather indefinite type of distress until eight months prior to her coming to the clinic when she had noticed that the symptoms had become more intense about three hours after meals. At a later time a gnawing, burning pain had developed and had been relieved after she had drunk a glass of milk. During the time of maximal distress, sour material, which occasionally had contained fresh blood, frequently had been regurgitated. The Wassermann reaction was negative. Fractional gastric analysis after a test-meal revealed persistent achlorhydria, and total acidity ranging between 8 and 14. A total of 164 c c of gastric content was aspirated. Roentgenologic examination revealed persistent narrowing of the pyloric end of the stomach. At operation an inflammatory area 2 cm in diameter was found just above the pylorus. When this area was excised, it was found to be the site of localized interstitial gastritis.

*Comment on gastritis*—The ratio of males to females in this group was 15/6. The average age of the patients was forty-seven years. The duration of symptoms was variable, ranging from ten days to thirty-five years. In one case in which the history was fairly definitely of the type obtained in cases of ulcer and dated back thirty-five years, ulceration was not demonstrable, instead diffuse duodenitis and diffuse gastritis were found.

The cases in which gastritis is found associated with gastric or duodenal ulcers present syndromes that usually have definite characteristics of ulcer. Even in these cases, however, there may be a tendency toward distortion of the usual picture obtained in ulcer. The symptoms of gastric ulcer frequently lack the definiteness of duodenal ulcer. In those cases in which

gastric ulcer is associated with gastritis or duodenitis, there is still further departure from the usually approved syndrome of peptic ulcer, there is less tendency toward remission, there is less noticeable localization of pain, frequently there is a definite qualitative relationship to the taking of food, there is some complaint of belching and bloating, and a diffuse sensation of discomfort in the upper part of the abdomen which may reach maximal intensity from thirty minutes to two hours after meals. Food and soda relieve this discomfort less consistently than in cases of peptic ulcer.

In cases in which gastritis is not associated with ulceration, the history is even more irregular, usually, however, it still maintains some characteristics suggestive of peptic ulcer. There is a noticeable similarity between the complaints registered by these patients and that rather ill-defined syndrome of complaints designated as a "gall-bladder reflex." Generalized discomfort in the upper part of the abdomen, nausea, belching, bloating after heavy meals or after meals which include much greasy or fried food, vomiting, and pain radiating from the epigastrium through to the back are symptoms which frequently are noticeable in these histories. Included in the symptoms, however, there is usually something suggesting a peptic lesion, there may be intensification of distress several hours after meals, relief or some tendency toward remission of the more severe symptoms is afforded by food or soda.

The pain described by these patients is extremely variable and it comes on at irregular times after meals. The

distress may not reach maximal intensity until several hours after the ingestion of food. Although the pain in most instances is not severe, it occasionally is so intense that a penetrating peptic ulcer is assumed to be present.

Gastric acidity is usually low. In one of these cases, however, total acidity of 112, and free hydrochloric acid of 80 were reported. Total acidity of more than 70 was found in only three instances. In all of these cases duodenal ulcer was found to be present in addition to gastritis. In one of the remaining cases, the total acidity was above 60. At operation in this case an area of duodenitis and diffuse gastritis was found. Total acidity below 30 was found in 33 per cent of the cases included in this group, in 23 per cent there was achlorhydria. The lower the acids, the less probability there is of finding ulcer associated with gastritis, and incidentally the lower the acids the less likelihood there is of finding in patients with nonulcerating inflammatory gastric lesions a syndrome of the type found in ulcer. The roentgenographic data in these cases were not of great help in arriving at a diagnosis except in that they helped to localize the pathologic process.

There is a decided divergence of opinion regarding the significance of the diffuse and of the localized inflammatory lesions of the stomach. That syndromes which lead to operation at times are solely attributable to these nonulcerating areas of inflammatory gastric reaction seems to demonstrate that these lesions can be of clinical significance. Patients with definite symptoms, including hemorrhage or obstruction, are not infrequently re-

lieved of all their complaints following excision of an inflammatory lesion in the wall of the stomach. Exact classification of such lesions by the pathologist is not always possible. The responsibility for making a decision regarding the malignancy or benignity of the lesions, preoperatively, is frequently extremely disquieting and involves a risk which but few would be willing to take. Not infrequently the severity of the complications, the bizarre quality of the complaints, the low gastric acidity, the appearance in the roentgenogram of an aberration from the normal gastric contour, and the rather advanced age of the patient makes it extremely hazardous to advise any therapeutic measure other than surgical exploration.

The differential diagnosis in these cases seemed invariably to resolve itself into the consideration of whether or not the lesion is malignant. A satisfactory preoperative differential diagnosis is often impossible. Occasionally spasm involving the pylorus and extending upward will produce a deformity which may be persistent, and which may simulate intrinsic gastric disease. This at times is found to be a reflex phenomenon resulting from an ulcer elsewhere in the stomach, and I have seen instances in which such spasm disappeared after a diseased appendix or gallbladder had been removed.

Linitis plastica is another condition which may produce a clinical picture simulating this condition. At one time the term linitis plastica included all the conditions of hypertrophy and induration of the gastric wall not obviously malignant. This lesion is rare. At the present time there is a tendency toward

restricting the term to cases in which small-cell carcinoma is found. It seems practically impossible to distinguish, preoperatively, benign inflammatory gastric lesions from malignant linitis plastica. The symptoms are similar, although in linitis plastica the loss of weight is usually greater and the duration of symptoms shorter. The average age of the patients in the group with linitis plastica was found by Lyons, in 1924, to be fifty-two years. This is five years older than the average age of the patients with localized or diffuse gastritis.

Gastric syphilis is another lesion which may have to be considered in the case of gastritis. Roentgenologic examination in gastric syphilis and in gastritis reveals similar deformities. In the presence of reliable evidence of syphilis elsewhere in the body or of a positive Wasserman reaction, it would be impossible, except by a therapeutic test or by microscopic investigation of tissue, to be certain which lesion was present. The latent possibility of a malignant condition, especially if serologic evidence is negative, makes it safer to perform exploration. Vacillation between diagnoses may jeopardize the chance of saving human life.

#### GASTROPEJUNITIS

Occasionally ulcerating or nonulcerating inflammatory reactions are demonstrable about the site of gastroenterostomy performed for the cure of peptic ulcer. The complication, although rare, becomes of formidable significance once it has developed.

This group of cases offers perhaps the best opportunity to study the clinical manifestations of benign inflammatory peptic lesions. In duodenal or gastric

ulcer, the time of onset frequently cannot be determined with any degree of accuracy, nor consequently can the early symptoms of the developmental stage be accurately designated. There is a distinct period of time preceding which it is not likely that stomal lesions will form, only with the performance of gastro-enterostomy was the soil prepared on which these lesions could possibly develop.

The developmental cycle of benign inflammatory lesions involving the stoma has not been definitely established. The similarity existing between stomal and duodenal lesions is striking. Similar pathologic processes and similar syndromes are readily recognizable in these histories. That the same etiologic factors are responsible for both lesions seems more than probable. In this series three types of lesions are distinguishable: the localized inflammatory process without a break in the mucosa, the same process with shallow ulceration, and the well developed gastrojejunal ulcer with a definite crater, and associated nonulcerating gastrojejunitis. That these conditions are merely different stages of the same developmental process, and that gastrojejunitis is frequently the forerunner of gastrojejunal ulcer is a reasonable suggestion, but evidence seems still to be insufficient to establish this sequence as a proved fact. What seems of equal importance, however, is the fact that such lesions can produce distinct syndromes, even though ulceration is not demonstrable at operation. Nor does it seem logical to assume that the operative findings represent anything but the true pathologic appearance of the lesion producing the symptoms because

surgical intervention was undertaken in some of these cases during the maximal intensity of symptoms.

*Case 8* Nonulcerating areal gastrojejunitis. A man, aged forty years, had begun to have dyspepsia, with definite characteristics of peptic ulcer, at the age of thirty-one years. Hemorrhage or attacks characteristic of perforation had not occurred. At the age of thirty-three years he had been operated on elsewhere and a duodenal ulcer had been found. Gastro-enterostomy had been decided on as the procedure of choice. For three months following the operation he had remained well. Then recurring difficulties similar to those experienced before the operation had developed. In addition to the epigastric distress which had come on several hours after the ingestion of food, by the time he came to the clinic he was experiencing at intervals pain at a site lower than the original situation of the distress. Nevertheless, the symptoms still maintained the sequence of pain, food, ease. The pain frequently had been referred from the umbilical region, through to the back. On a few occasions he had vomited blood in small amounts. When he consulted the clinic, the roentgenologic examination disclosed evidence of duodenal deformity and of a normal stoma. Analysis of gastric content revealed total acidity of 48 and free hydrochloric acid of 28, 275 cc of content was recovered. At operation, an old duodenal ulcer and multiple jejunal ulcers were found. The ulcers were excised. Posterior gastro-enterostomy was performed. Six months after this operation trouble referable to the stomach had again appeared. The distress was at its maximum about three hours after meals. The site of pain was about 75 cm below the umbilicus in the median line. Soda gave prompt relief from the distress. At times he had intervals of three to four months when he felt well. Four years after the operation, following a brief period of recurrence of symptoms, he vomited a large quantity of blood. A year later he had a similar experience. He again returned for examination and at this time the roentgenologists reported a

jejunal ulcer with obstruction Analysis of the gastric content revealed total acidity of 22 and free hydrochloric acid of 10, 145 c c of gastric content was recovered At operation an ulcer was not found but there was a definite area of inflammation about the stoma A posterior Polya type of operation was performed, with complete relief of symptoms

*Case 9* Areal gastrojejunitis with shallow ulceration A man, aged fifty-five years, had submitted to gastro-enterostomy for duodenal ulcer eleven years before consulting the clinic For eight years prior to this operation there had been intervals of dyspepsia which had been characteristic of peptic ulcer A few attacks associated with melena and hematemesis had occurred For about six years after the operation the patient had felt well, then, without any warning he had vomited some blood and had noticed tarry stools For several years following this experience he had had intervals of several weeks during which he had had mild distress in the epigastrium two to three hours after meals This had disappeared after the ingestion of food For three years he had had intervals of distress, and then, for eight years, he had been free from any gastric upset Eleven years after the first postoperative hemorrhage he had had a second, and shortly thereafter, a third Then there had ensued a period during which he again had had distress in the epigastrium several hours after meals There had been much gas and bloating associated with the pain When he came to the clinic he said that the pain was in the epigastrium, it was not very severe There was some regurgitation of sour material during the time of maximal distress Roentgenologic investigation at the clinic revealed stomal as well as duodenal deformity Titration of gastric content showed total acids of 40 and free hydrochloric acid of 20, 500 c c of content was recovered At operation, duodenitis and gastrojejunitis were found Partial gastrectomy was done The pathologist reported an area of gastrojejunitis in which a small shallow break in the mucosa was demonstrable

*Case 10* Gastrojejunal ulcer with areal jejunitis, duodenitis A man, aged twenty-six years, stated that trouble with his stomach had begun when he had been about fifteen years of age After a particularly severe siege of dyspepsia, gastro-enterostomy had been performed elsewhere for duodenal ulcer For two years following this operation he remained well Then the dyspepsia had reappeared The distress had been situated definitely lower than the site of the original pain, by the time the patient was seen at the clinic it was slightly below the umbilicus The pain radiated from this region downward into the lower left abdominal quadrant The distress reached maximal intensity from two to four hours after meals Food or soda did not relieve the pain consistently

Much fullness and bloating were associated with the pain The distress, he said, was intensified when he was riding on a wagon Frequently he regurgitated small amounts of sour material, usually at a time when he was having considerable pain Estimation of gastric acidity gave values of 73 for total, and 60 for free hydrochloric acid There was definite evidence of periapical infection and the tonsils were large and infected Roentgenologic examination showed evidence of a gastrojejunal ulcer At operation a perforating gastrojejunal ulcer and an area of gastrojejunitis were found There was also an area of duodenitis

*Comment on Gastrojejunitis* Histories of thirteen cases were included in this study, although only three are recorded The ratio of males to females in the group was 12:1 The ratio of males to females in the cases in which gastrojejunal ulcer was present was 15:1

The average duration of symptoms attributable to gastrojejunitis or to gastrojejunal ulcer with gastrojejunitis was eighteen months This relatively short duration of symptoms is probably attributable to the fact that practically all the patients included in this group

consulted the clinic because of the complications of gastro-enteric hemorrhages. There are, of course, no symptoms which will cause a patient to seek advice more promptly than the vomiting of blood or the passing of blood by bowel.

In cases in which there is an ulcerating jejunal lesion besides the jejunitis, the symptoms simulate the syndrome usually attributable to gastrojejunal ulcer. The pain is almost universally lower than that experienced with the original lesion in the duodenum. Patients with only a small area of inflammation involving the stoma may experience very severe pain, and this is in the area usually involved with stomal ulcers. In one of these patients, all of the pain was just above the symphysis pubis, the pain had the usual characteristics of ulcer in that it came on late after meals and was relieved by the ingestion of food. Occasionally the pain was referred through to the back. The reason for this symptom is probably the fact that most of the jejunal lesions are found, at operation, to have involved the jejunal wall rather deeply.

Patients with gastrojejunitis without ulceration usually complain of much flatulence in association with the pain. There is less tendency to remissions and less relief from the taking of food or soda than in those patients who have gastrojejunal ulcer. A few patients complained that certain types of food, such as fried foods, definitely precipitated symptoms. Surgical operation usually was advised for these patients because of repeated hemorrhages. Marked bleeding was at times noticeable when only small shallow

lesions were demonstrable at operation. In all but one of the cases included in this series the original ulceration for which gastro-enterostomy had been performed was in the duodenum. In the one exception, evidence of ulcer in the stomach or duodenum was not found at the time of the second operation.

The preoperative distinction of gastrojejunitis from gastrojejunal ulcer usually is impossible. From the analysis of the small group of cases available for study a definite syndrome cannot be formulated. Symptoms of great severity and of grave importance occasionally are observed when only a small nonulcerating inflammatory lesion of the jejunum can possibly be held responsible for the complaint.

In all of these cases definite foci of infection were found. Almost invariably cultures made from these foci, when injected intravenously into experimental animals, resulted in the formation of acute inflammatory lesions in the upper part of the gastro-intestinal tract. These lesions bore striking similarity to the lesions found about the stoma made at gastro-enterostomy in the human being.

#### COMMENT

The analysis of the histories of cases in which patients were found at operation to have nonulcerating duodenitis, gastritis, or gastrojejunitis revealed formidable syndromes of definite clinical significance. That the symptoms can be of severity equal to those experienced by patients who actually have peptic ulcers seems a significant fact. The average duration of symptoms was slightly less than eight years, thus

would appear to be ample time for ulcer to form if ulcer must necessarily be the final stage of development of these lesions

A review of the cases of duodenitis and gastrojejunitis revealed a parallelism in the characteristics of the two conditions. This resemblance continued through to many of the minutest particulars, histories, syndromes, complications and pathologic specimens maintained almost identical characteristics in most instances.

In these cases of inflammatory lesions there are usually some irregularities in the histories which distinguish the cases from those of uncomplicated peptic ulcer. There is usually less consistence, less clean-cut definition of symptoms, less tendency to remissions, more quantitative and qualitative relationship to the taking of food, and more admixture of the so-called gallbladder reflex in the usually approved syndrome of ulcer. Moreover, in diffuse inflammation of the duodenum, the pain has a tendency to be referred to the upper right quadrant of the abdomen. In uncomplicated duodenal ulcers, the tendency is for the pain to be fairly well localized to the mid-epigastrium. On the other hand, in the subacute types of ulcer, with deep penetration into the duodenal wall, the distress is so frequently localized to the right of the median line, that in 37 per cent of the cases a pre-operative impression of associated cholecystitis was added to the diagnosis of duodenal ulcer, and this despite the fact that roentgenologic examination gave definite evidence of duodenal ulceration, and the clinical history in-

cluded otherwise characteristic syndromes of ulcer.

Symptoms of gastrojejunitis exhibit some similarity to those usually found in gastrojejunal ulcer. The distress is almost invariably described as definitely lower in situation than that caused by the original lesion in the stomach or duodenum. The analysis of the histories of cases of patients having only nonulcerating jejunal lesions gives one the impression that there is usually a little less regularity in these histories than in those of cases in which there are associated gastrojejunal ulcers. The distress comes more irregularly after meals, it is not so consistently relieved by food, there is much associated bloating and flatulence, and there is but slight tendency toward remission.

In cases of gastric ulcer, particularly in those in which there is hypochlorhydria or achlorhydria, the history is frequently indefinite. There is still a greater departure from the usual syndrome of ulcer in those cases in which there are nonulcerating inflammatory gastric lesions. At times there is but a vague suggestion of benign peptic lesions in the complaints registered by these patients. If it were not for the fact that severe pain or hemorrhage is sometimes included in these complaints, and for the discovery by roentgenograms of some irregularity in the gastric contour, certainly the presence of many of these lesions would never have been suspected.

The symptoms of gastric hemorrhage not infrequently produce problems very difficult to solve. The indeterminate gastro-enteric hemorrhage frequently can be explained by the dis-

covery at operation of one of the rather innocuous appearing duodenal lesions. Occasionally, bleeding is the only symptom exhibited by these pathologic processes.

Certain indefinite syndromes may often be found. They may present a few symptoms suggestive of disease of the gallbladder and a few of the characteristics usually attributable to peptic ulcer, yet definite physical findings may not be exhibited and roentgenologic aberrations may not be found to be attributable to localized or diffuse duodenal lesions.

The presence of foci of infection in most of the patients who harbor areas of duodenitis, gastritis, and gastrojejunitis, and the similarity of these areas of ulcerating and nonulcerating lesions to those experimentally produced in animals, would seem to argue in favor of accepting infection as the most frequent cause in producing the original trauma responsible for these lesions. At least it would seem hazardous to ignore the presence of definite foci of infection when these gastro-enteric lesions are suspected or have been shown to be present.

Thorough collaboration of surgeon, pathologist, roentgenologist and clinician in the systematic investigation of these lesions undoubtedly would result in clarifying knowledge concerning them. Early recognition of the lesions undoubtedly would obviate much suffering and might prevent the development of some very grave complication.

The developmental cycle of gastroduodenal lesions is not fully understood. The probability suggests itself that the same lesion undergoes mutation into various forms. Not infre-

quently the same specimen exhibits all the pathologic stages in which these lesions have been observed. In certain instances, small, innocuous appearing inflammatory lesions were found to be productive of definite symptoms, including hemorrhages, in other cases, careful microscopic investigation was necessary before slight breaks in the mucosa were detected, in still others, shallow ulcerations were easily detectable. Then again, there were others which presented well developed or acute chronic ulcers situated as craters in the midst of a definite inflammatory area.

Whether there is an etiological relationship between these lesions and chronic peptic ulcer is still an undecided question. More evidence is constantly adduced to suggest that the developmental cycles of peptic ulcer, and of the nonulcerating inflammatory peptic lesions, proceed jointly over the earliest part of their formative period. After the development of the original lesion, certain factors which may be present, or which may arise periodically, decide the course, the condition may remain stationary as an areal inflammatory lesion or it may heal rapidly, in other instances the condition may go on to a more extensive, nonulcerating inflammatory lesion, involving all the coats of the gastric or duodenal wall, occasionally it finally results in localized areas of necrosis, with acute ulceration.

Peptic ulcer, in most instances, is probably the result of a succession of preliminary changes in tissue. A single cause, such as infection, can be sufficient to produce acute and probably even chronic ulcer, as Rosenow has



shown In most instances, however, the establishment of a chronic ulcer is probably the result of a combination of causes

The development of peptic ulcer can be represented as passing through two stages first, the stage of trauma, which includes the period during which the original aberration from the normal histologic arrangement of tissues takes place, and second, the stage which includes the period during which conversion of the original lesions into a chronic ulcer is accomplished

The factors which are responsible for the stage of trauma may be entirely inadequate in themselves to accomplish the transition of these original lesions into chronic ulcers On the other hand, probably the circumstances responsible for the conversion of these preliminary lesions into chronic ulcers would not be effective in instituting the original formation of these same lesions It is conceivable that at times the secondary requirement for the establishment of chronicity in ulcer can antedate the formation of the original lesion and may even be productive of a syndrome suggesting ulcer, prior to its development Various hypotheses have been advanced to explain the intimate mechanisms which militate in the establishment of chronicity in ulcer

A clinical observation might here be in order There are certain types of patients of the nervous, intensive, tenacious and high-strung, driving type who seem predestined for the development of peptic ulcers Repeated efforts to cure these patients by the usual medical methods fail and surgical efforts occasionally seem merely to furnish additional soil whereon new ulcers

develop In a paper on recurring peptic ulcer, these patients have been referred to as "the recurring ulcer type"<sup>9</sup> There is some variability in the degree of these psychophysiologic tendencies in the same individual at different times, and it is entirely possible that this variability has much to do with the determination of the element of periodicity in chronic ulcers At the present time data are being accumulated in an attempt to show that in many instances the period of active symptoms follows or accompanies unusual nervous or physical strain Not infrequently patients who present the nervous tendencies described complain of symptoms characteristic of ulcer, yet they fail to show, even after the minutest inspection of gastric or duodenal tissues, any evidence of ulcer The question then naturally arises whether the accepted syndrome of ulcer is invariably due to ulcer, or whether it may not be due to a physiologic or neurogenic aberration which results in disorders of motility and secretion, which, in turn, result, for example, in pylorospastic phenomena, attributed by some authors to parasympathetic hypertonus

These same mechanisms, in conjunction with factors which are potential in influencing the stage of trauma, such as focal infection, could be the determining factors responsible for various pathologic changes in the lesions described in this paper They could easily be the determining factors in deciding whether chronic ulcers shall develop from these lesions

Somewhere within the mechanism which influences the sympathetic and

parasympathetic control of the upper part of the gastro-intestinal tract is a wealth of information which will need to be understood before the final word regarding the etiology of ulcer will have been spoken

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# Pernicious Anemia: The Behavior of Various Extracts of Stomach and Duodenum Used to Induce Remissions\*†

By ELWOOD A. SHARP, M.D., RICHARD M. MCKEAN, M.D.,  
and ELMORE C. VONDER HEIDE, M.D.,  
*Detroit, Michigan*

IN September, 1929, one of us (E. A. S.)<sup>1</sup> reported the presence of an antianemic factor in desiccated hog stomach. The clinical evaluation of these stomach preparations in pernicious anemia was described by Sturgis and Isaacs<sup>2</sup>, and later by Renshaw<sup>3</sup>. Subsequently, the value of stomach tissue in this disease was confirmed by Connor<sup>4</sup>, Wilkinson<sup>5</sup>, Geuting<sup>6</sup>, Godel<sup>7</sup>, Jagic and Klima<sup>8</sup> and others, working independently.

Since the ratio of dried gastric tissue to raw substance is low, thereby entailing the daily use of 20 to 40 gm of desiccated substance to induce a remission in pernicious anemia during a severe relapse, efforts have been made to isolate and concentrate the active principle contained in stomach tissue as well as to search for antianemic properties in other visceral tissues.

Wilkinson<sup>5</sup> and Isaacs and Sturgis<sup>2</sup> have found gastric mucosa possesses slight antianemic activity. Wilkinson

fed 250 gm of raw mucosa daily and caused a rise of reticulocytes. Isaacs and Sturgis used 30 to 60 gm of dried mucosa daily in pernicious anemia and found only slight stimulation of reticulocytes and negligible red blood cell regeneration.

At the earliest inception of this work the mucosa stripped from the central glandular area of swine stomachs was selected as a possible source of the blood-maturing substance effective in Addison's anemia. The raw tissue was prepared for oral use by desiccation at a low temperature. This preparation given in daily doses of 30 gm, representing approximately 150 gm of raw tissue was found, however, to have no appreciable erythropoietic activity. Subsequently these patients had satisfactory remissions induced by the use of desiccated whole hog stomach. It was assumed then that the mucosa of swine stomach required the presence of the other gastric tissues to activate its antianemic factor or that that factor existed only in the discarded portion. Up to the present time it has been impossible to disprove or confirm either hypothesis.

\*From the Metabolism Section, Receiving Hospital, Detroit, Mich.

†Material furnished by Parke, Davis & Company.

### THE LIPOIDAL EXTRACT OF STOMACH TISSUE

From a study of two patients, presumptive clinical evidence indicated that stomach tissue completely defatted had a reduced hemopoietic activity in pernicious anemia. Since this viscus contains abundant complex phospholipins readily extracted by acetone, a lipoidal fraction was obtained from dried whole stomach in order to ascertain if the active principle could be isolated in this manner. The lipoidal extract was evaporated to dryness and each gram of the solid lipid remaining at the end of the

process was found to represent 75 gm of raw material. Suitable patients were given 6 to 9 gm of the lipid daily for 11 days, but there were neither hematologic nor general physical signs of improvement at the end of this period of observation.

It is improbable that any effective blood-maturing principle can be obtained by this method, although in dealing with an unknown substance we do not feel warranted in arriving at a definite conclusion from meager data. Nevertheless, the inactivity of the gastric tissue completely defatted, coupled with an entirely negative

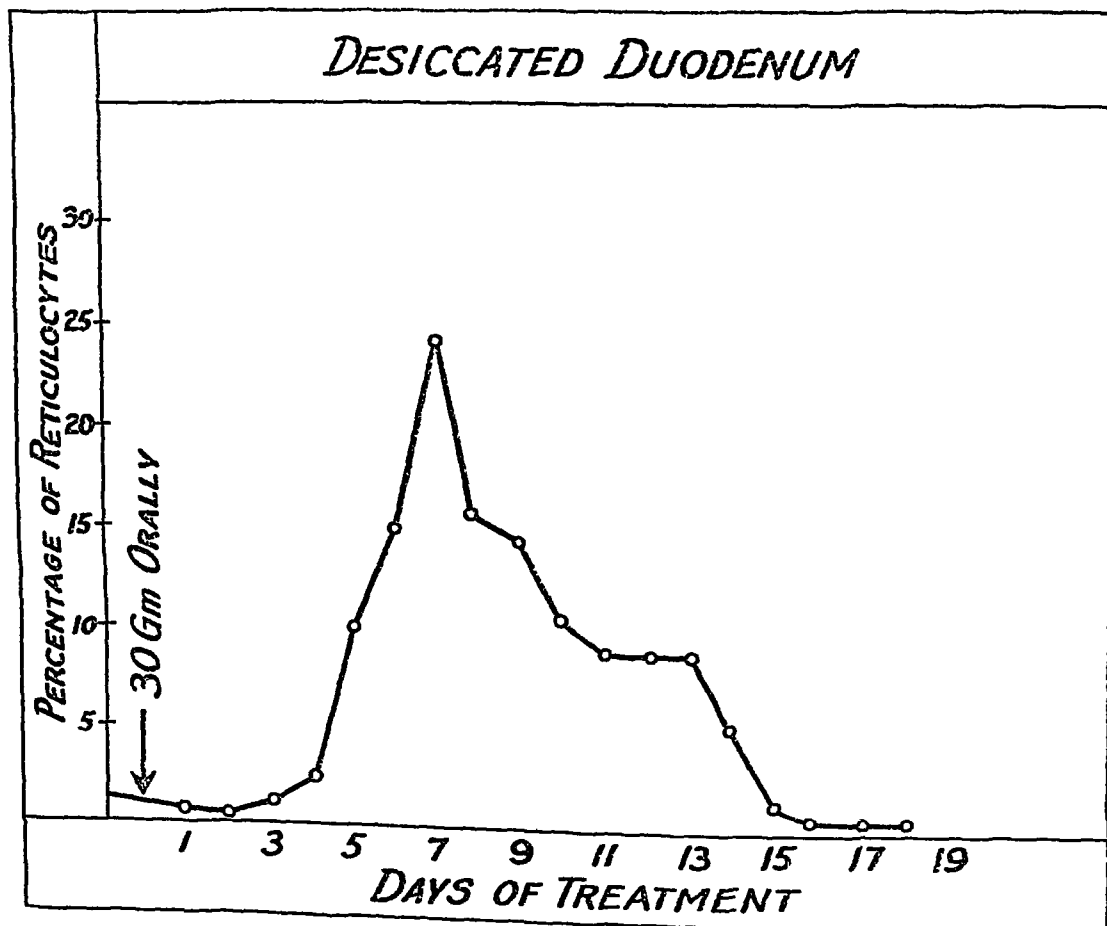


CHART I The "reticulocyte response" after feeding dried duodenum (representing 250 gm of fresh substance) was 24.8 per cent. The calculated rise of reticulocytes for the anemic substance is adequate

hemopoietic response after the use of its extracted lipid, connotes injury to or destruction of the active principle

THE USE OF DESICCATED DUODENUM IN PERNICIOUS ANEMIA

Desiccated duodenal tissue obtained from swine, given in doses of 30 gm daily (representing about 250 gm of raw substance), has been used to induce remissions in pernicious anemia. In one patient having a severe relapse it will be seen (Chart 1) that the reticulocyte response measures up to the criterion used for determining the potency of antianemic substances. The symptomatic improvement of this pa-

tient was immediate. The red blood cells rose from 1,300,000 per cu mm at the beginning of treatment to 3,200,000 per cu mm at the end of the third week with a proportionate improvement in hemoglobin. It is rational to suggest, therefore, that duodenum possesses about the same degree of blood-maturing power as stomach tissue.

REMISSION INDUCED BY THE RECTAL ADMINISTRATION OF STOMACH TISSUE

A rapid remission of pernicious anemia has been induced by the rectal administration of 30 gm of desiccated

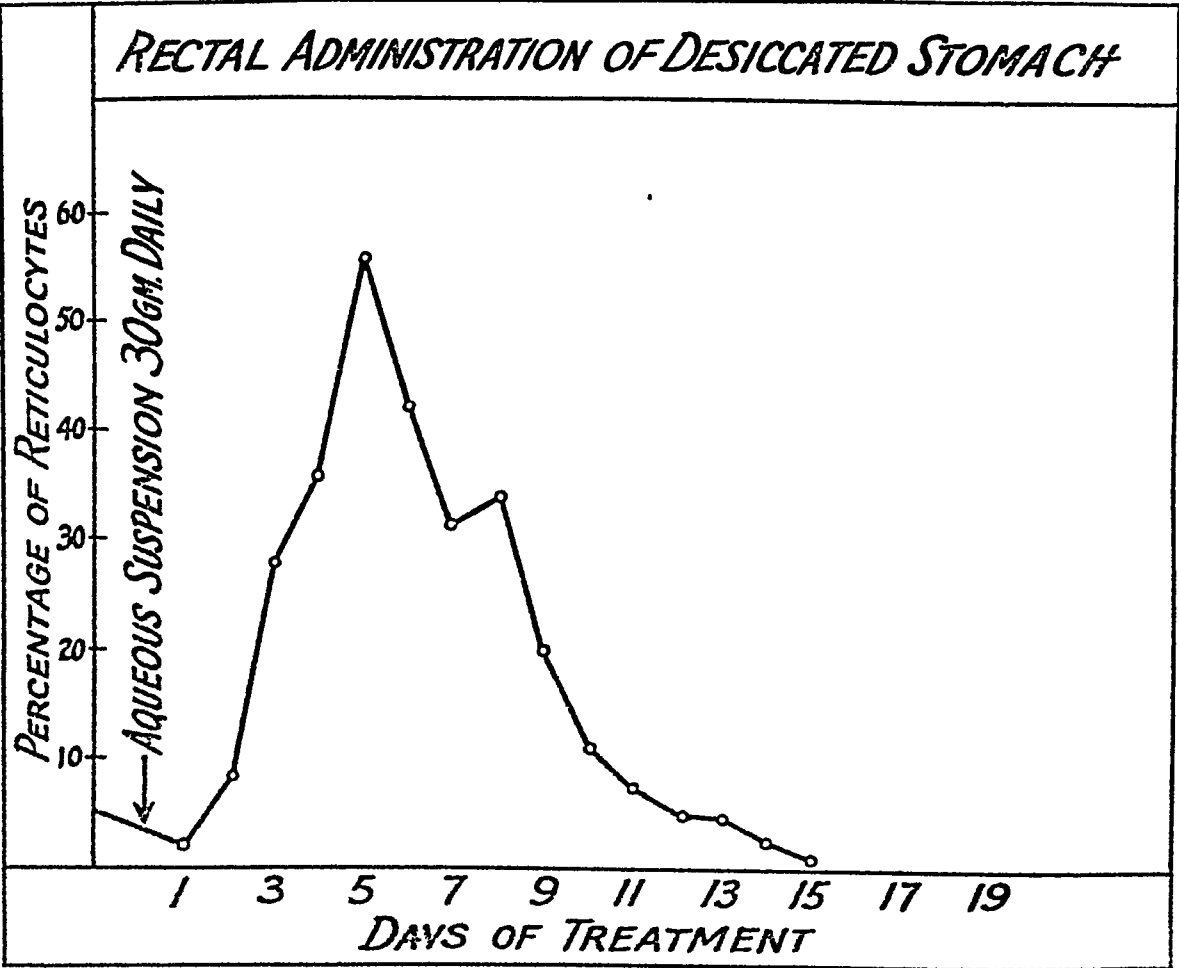


CHART 2 The "reticulocyte response" after rectal administration of an aqueous suspension of Ventriculin 30 gm daily was 51 per cent. The calculated reticulocytosis for the initial count of 800,000 red blood cells is 41.6 per cent.

stomach tissue in aqueous suspension. This patient was mentally deranged, therefore only an occasional teaspoonful of stomach tissue probably less than 10 gm, could be given orally during the first 48 hours of treatment. At the end of 96 hours the reticulocytes had reached a concentration of 54 per cent (Chart 2). The phase of reticulocytosis was followed by satisfactory red blood cell maturation, the red blood cells increasing from 800 000 per cu mm at the beginning of treatment to 2 400 000 per

cu mm on the fourteenth day. This procedure has been carried out subsequently in several patients with less remarkable results but is still under investigation.

#### EFFICACY OF AN AQUEOUS EXTRACT OF DRIED STOMACH

The significance of the apparent utilization of the antianemic factor when given rectally is not obvious. The observation gave rise, however, to further speculation regarding the char-

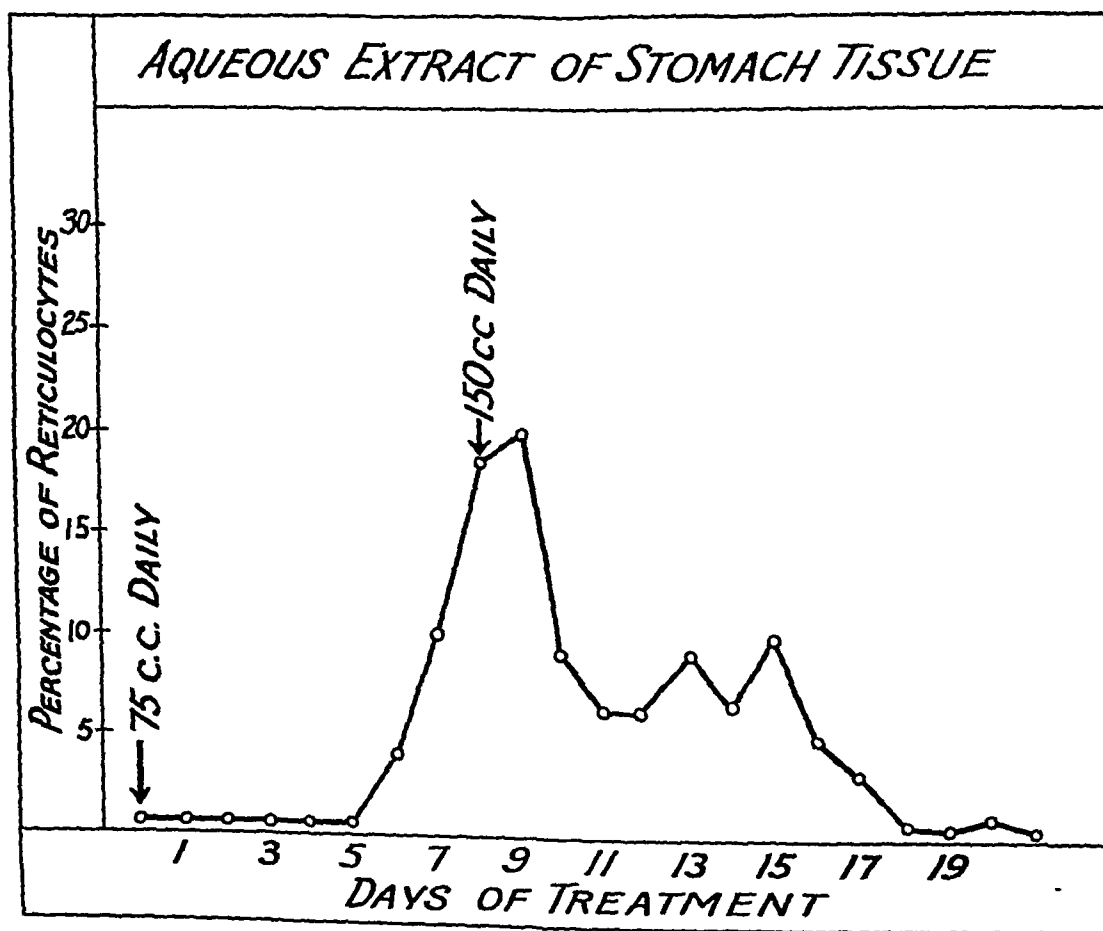


CHART 3 The "reticulocyte response" obtained by the oral use of 75-150 cc of aqueous stomach extract (representing 45-90 gm of dried tissue) was 21 per cent exceeding slightly the expected reticulocytosis of 17.1 per cent. The character of the plateau in the charted curve suggests that the "peak" may have been missed or an additional stimulation of reticulocytes occurred when the dosage was increased.

acter of the active substance. It was assumed that an aqueous filtrate derived from stomach tissue might contain the active principle, since it was apparently liberated and absorbed in the rectum when given in aqueous suspension. The action of digestive juices on ingested desiccated tissue heretofore used was considered essential for effective therapy. This view may have to be modified owing to the rapid induction of remissions in four patients following the oral use of an aqueous extract of desiccated stomach substance. The satisfactory remission induced in the first patient studied (Chart 3) has been repeated by using 75 cc of the filtrate daily—as was done initially. This amount of filtrate represents approximately 45 gm of dried stomach tissue, hence a fairly large yield of the active principle is obtained by this simple method.

The maximum reticulocytosis of 21 per cent, occurring on the fifth day after treatment was started, must be regarded as evidence of effective

therapy, since this percentage of immature red blood cells is in accordance with the calculated ratio to red blood cells described by Minot and his associates and as modified by Riddle<sup>10</sup>

#### COMMENT

The nature of the specific factor present in gastric tissue promoting red blood cell regeneration in pernicious anemia is still obscure.

The lipoids extracted from stomach tissue do not possess antianemic properties.

The existence in duodenum of an antianemic factor has been suggested, although there is no evidence so far adduced to warrant the belief that it is more effective than gastric tissue.

The liberation and utilization of the antianemic principle of stomach substance, when given in aqueous suspension rectally, led to the study of aqueous filtrates for oral administration. These filtrates are apparently highly effective for the induction of remissions in Addisonian anemia.

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# Arthritis of Cerebral Origin

By KARL ROTHSCHILD, M D, *New Brunswick, N J*

THE classification of the various forms of arthritis has lately been simplified so that at the present time, we have only to distinguish between hypertrophic and atrophic arthritis<sup>1</sup>. In this classification are included cases of acute infectious arthritis, of chronic infectious arthritis and those cases in which a toxic element is considered to be of etiological significance.

With all due consideration for the simplicity of this classification, there is a certain number of cases which show definite arthritic changes but will not fit into any of the above mentioned classes. There are cases where, nolens volens, we will have to assume that the arthritic conditions are of cerebral origin.

It is a general assumption that the calcium metabolism, as expressed in the amount of calcium present in 100 cc of blood, bears a certain relation to the formation of arthritic changes. Pemberton, however,<sup>2</sup> reaches the conclusion that "whereas there is an undoubted local disturbance of calcium metabolism in the immediate neighborhood of joints showing marked osseous change, and also more widely in the long bones following inactivity, this disturbance is not reflected in the fasting circulating blood at large". Mark<sup>3</sup>, on the other hand, publishes three cases of arthritis de-

formans where the blood calcium was found to be between 20.4 and 27.4 mgs per 100 cc. Weil and Guillaumin<sup>4</sup>, Watchorn<sup>5</sup> and Horowitz<sup>6</sup> report similar findings.

Considering the mechanism of activity in these cases, it should be borne in mind that the calcium metabolism is dependent on the parathyroid glands. Disturbances of these glands will alter the balance of this mechanism. The change may be of either quantitative or qualitative nature, the latter not being well understood at the present time. The parathyroid glands, like all the glands of internal secretion, form a very definite part of the autonomous nervous system. While the secretion of these glands is responsible for the balance of the endocrine functions throughout the body, we have to assume that these glands are, so to say, only the "factories" of those products, without themselves possessing proper control over the amount and quality of the output. In order to regulate this output, its amount and its variation under changing conditions, we have to accept the theory of the presence of a higher regulatory center, located in the brain. Our cortex, in a general way, is an organ producing inhibitions, which means that the coordination and limitation of originally unorganized or excessive motions or emotions, originating in phylogenetically older cen-



teis, are produced by cortical centers. The presence of such a higher center has so far been proven for sugar metabolism.

In his recent article on "Sleep as a problem of localization"<sup>6</sup>, v Economo mentions the work of Mingazzini and Barbaia, who claim that "during the waking state the action of the excitokatabolic sympathico-tonic hormones of the thyroid, the suprarenals, the gonads and the hypophysis predominate, but that during sleep the excitoblastic stimuli influencing the tonus of the autonomic system gain control". As a consequence of encephalitis, he continues, we find, "changes of sleep in different directions, sopor, insomnia, inversion of sleep, dissociation of sleep". These changes must bear a relation to the anatomical findings of those cases, which occur in the infundibular region. "That influence is effected directly on the neighboring vegetative centers, as for instance the centers of temperature, for sugar and calcium content of the blood, etc., which all change during sleep and the centers of which are located in the subthalamie region and in the wall of the third ventricle". Thus it appears that there is a center for calcium metabolism located in the region of the gray matter around the third ventricle. There may be a higher center yet, controlling the interrelations of all the endocrine glands, but for the purpose of this paper it suffices to demonstrate the presence of the above described center for calcium regulation.

While making a study of several families suffering with Huntington's chorea<sup>7</sup> at the Psychiatric Hospital in Heidelberg, it occurred to me that a

large number of those patients, independent of their age, showed definite arthritic deformities which we could not explain by the assumption of accompanying infectious or toxic arthritis, but for which we thought the disease itself to be responsible. Most striking were several cases, the hands of which appeared bent in the direction of the ulna in the wrist joints. Figures 1 and 2 will demonstrate the exact conditions. Both of these cases were members (uncle and nephew) of a Huntington's chorea family<sup>8</sup>. A full photograph of case 1 is reproduced (Fig. 3) in order to show a typical picture of the posture and muscular tonus of those patients. Later on, at the Neurological Institute of the University of Frankfurt, I saw several similar cases. This time, however, we were dealing not with Huntington's chorea but simply with "old people". These patients show very similar deformities of their hands (Fig. 4 and 5). It should be repeated that there were no traces of infectious arthritis present but all showed various degrees of lesions of the striate body system. On seeing those cases, one is reminded of arthritis deformans.

Another frequent sign of deformity is demonstrated in figures 6 and 7. The former depicts the hand of a girl of 19 years of age, suffering from mental symptoms attributable to Huntington's chorea. As will easily be seen, the little finger is incurvated and rather short, not even reaching to the joint connecting the central and distal phalanges. Figure 5 is a photograph of the hand of a young boy of 9 years of age, who already presents marked signs of beginning progressive chorea.

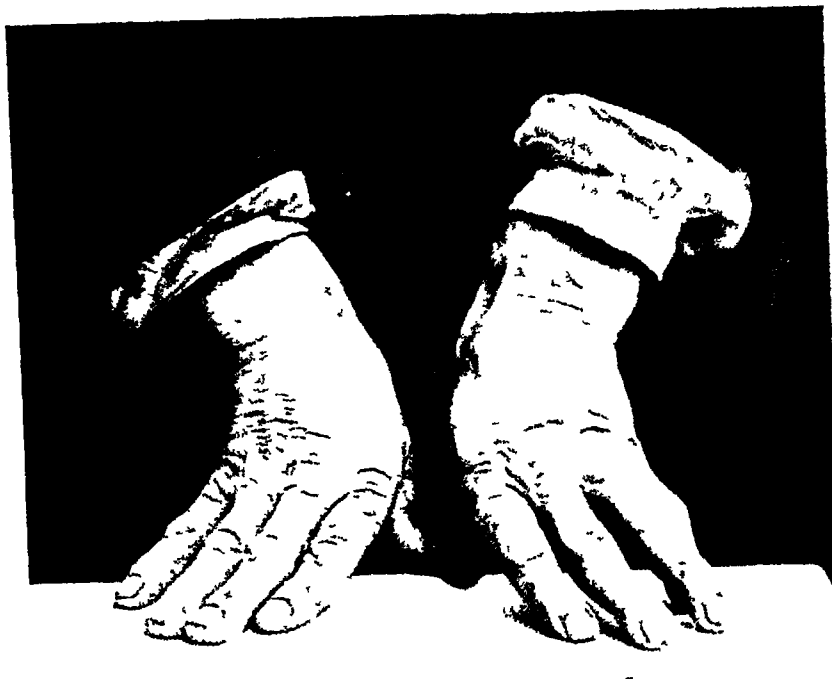


FIG 1 Hands of a case of Huntington's Chorea, showing excurvation of the wrist joints



FIG 2 Hands of a case of Huntington's Chorea (Uncle of Fig 1)

His father is a member of a Huntington's chorea family in which, besides himself, six brothers and sisters are affected<sup>7, 8</sup>. In this case, too, the shortness and incurvation of the little finger are well pronounced. Besides those cases reproduced, we have observed a number of deformities large enough to raise the observations above the level of coincidences.

In this connection, it may be worthwhile mentioning that a similar condi-

tion of shortness and incurvation of the little finger has frequently been described in cases of mongoloid idiocy<sup>10</sup>. For comparison with my final conclusions, I like to quote van der Scheer<sup>11</sup>: "The dominant finding is hypoplasia or a defect of development of the base of the cranium, of the gyri recti and of the *floor of the third ventricle*"

To my knowledge, there have been no exhaustive studies with regard to



FIG. 3. Same man as Fig. 1, showing increased muscular tonus and peculiar attitude.

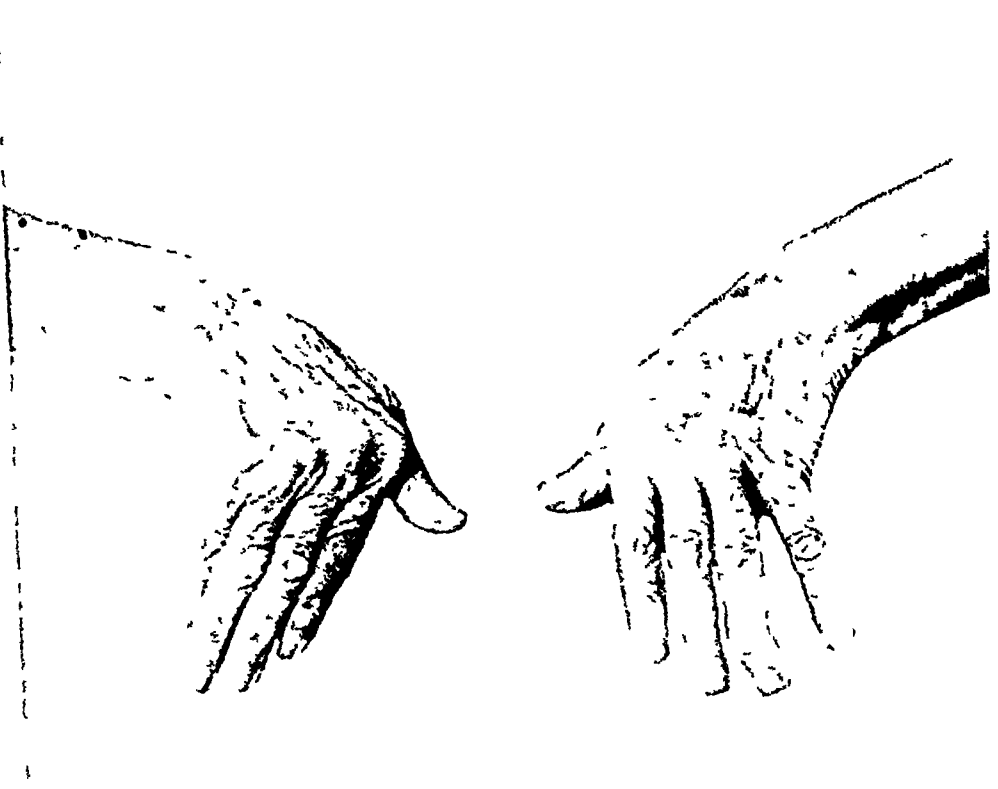


FIG 4 Hands of an old woman, with symptoms showing disease of the striate body



FIG 5 Case like Fig 4, deformities more pronounced

the metabolic activities in patients suffering from diseases of the striate body system. It is known that Wilson's disease is accompanied by cirrhosis of the liver. It is problematic which is the primary and which the secondary factor in the production of this ailment. Doll and Rothschild<sup>8</sup> have found polycythemia rubra and the presence of urobilinogen in the urine in a case suffering with Huntington's chorea.

Assuming that the deformities as shown are a part of the striate dysfunction syndrome and thus of cerebral origin, let us consider the mechanism

As v Economo has shown, changes of sleep and, accompanying it, changes in sugar and calcium metabolism, can be produced by lethargic encephalitis. This disease, as is now well understood, leads in its chronic form to degenerations in the striate system, the symptoms of which are known as Parkinsonian. The centers for sleep and calcium metabolism are located in the immediate neighborhood of these structures and are phylogenetically and ontogenetically of the same age as those bodies. Thus, it will not be difficult to understand that in the other



FIG. 6. Hand of a young girl of 19 years, showing shortness and incurvation of little finger (Huntington's Chorea). (Same family as Figs. 1, 2, 3)

disturbances of this region (chorea Huntington, chorea chronica, paralysis agitans, Wilson's lenticular degeneration and Westphal's pseudosclerosis), too the neighboring center for calcium distribution may be involved in the pathological process, producing "arthritis."

It might be in place to mention also that the increased muscle tone found in corpus striatum lesions may well be due to a disturbance of this calcium center. Figure 3 gives a good illustration of this particular finding.

As far as the chemical mechanism of this disturbance is concerned, there is no definite evidence for the exact method of working. It should be emphasized, however, that the majority of cases with "arthritis deformans"

show an increased amount of calcium in the circulating blood. As mentioned above, the lack of definite proof of infection or toxemia in those cases may well support the hypothesis that this disease is really a cerebral process, indicating "aging" of our phylogenetically old centers. The fact that Pemberton<sup>1</sup> did not find calcium increase in soldiers suffering from arthritis of long standing is a good point for our assumption that these cases must have been of infectious origin and may even serve as a point in the differential diagnosis of the two ailments. But one consideration should not be omitted. Even if there were no quantitative blood calcium disturbance, there is still the possibility of qualitative changes of the calcium metabolism,

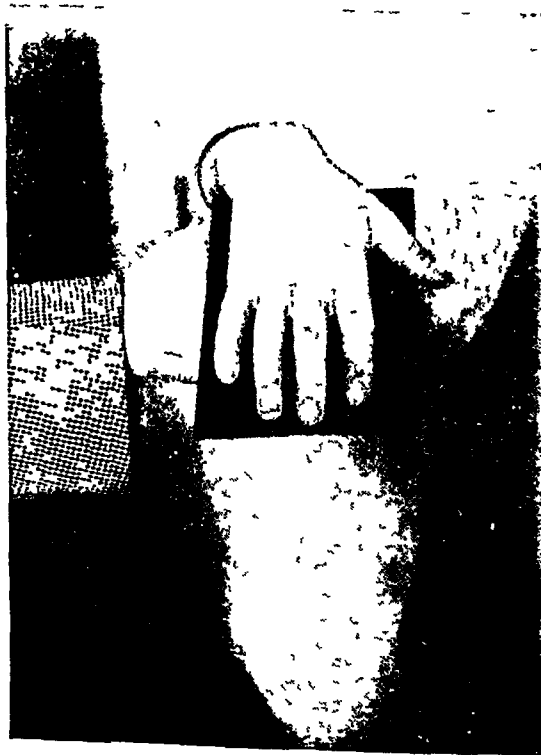


FIG 7 Hand of a boy of 9 years, (Huntington's Chorea), showing shortness and incurvation of little finger

possibly expressed in the interrelation between calcium and phosphorus balance. Our solely quantitative means of approach will not permit the detection of such abnormalities as yet.

*Conclusions* 1 Many cases of "arthritis" cannot be explained on the basis of infection or toxemia.

2 The center for calcium metabolism, located in the subthalamie region of the brain, in the gray matter surrounding the third ventricle, may be affected in the diseases of the corpus striatum system (chronic encephalitis, Huntington's chorea, chronic chorea,

paralysis agitans, Wilson's lenticular degeneration and Westphal's pseudo-sclerosis).

3 If this center is affected, there will be changes in the quantitative or qualitative calcium metabolism, producing "arthritis".

4 Arthritis deformans and possibly also mongoloid idiocy may be due to those disturbances.

5 Such arthritic changes in old people may be considered as "aging" of phylogenetically old centers, not involving the pyramidal tracts.

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# A Personal Experience with Diverticulitis of the Sigmoid\*

(A Study in Visceral Neurology)

By F M POTTENGER, M D , *Monrovia, California*

MY apology for detailing this personal experience is that it has furnished an unusual opportunity to apply the facts of visceral neurology to the study of the various symptoms, particularly the reflexes which may be caused by an inflammatory lesion in the colon and sigmoid. I did not have to take the indefinite answers of patients which often fail to convey the correct impression and which are difficult for the physician to interpret, but, furnished the answers myself, as they were manifested in my own body and perceived by myself.

When I came home from work in the evening of November 8, 1927, I noticed that I was somewhat more fatigued than usual. After eating dinner I did not feel quite comfortable. At ten o'clock I went to bed, but awakened at midnight with feelings of illness. I had a general discomfort through the lower half of the chest and upper portion of the abdomen, particularly the thoracic cutaneous zones Vth to IXth on both sides, as shown in fig 1A, which lasted for eighteen hours. It was not a severe pain but a very depressing sensation, much as though

I were held in a vice. Nausea and vomiting were present. The stomach contents expelled at midnight showed that the food was still undigested. Vomiting occurred twice later in the night. A diarrhea also followed. The temperature was elevated to 101°, and the pulse was slow. Coincident with this attack frequent eructations of small amounts of gas occurred, which became very annoying and persisted thereafter for months. This indication of a relaxed cardia increased in severity whenever the symptoms of acute diverticulitis were present, and has persisted until the present time.

A physician was called next morning who considered the possibility of the presence of an ulcer of the stomach, an appendicitis, or a diseased gall-bladder. Food and drink were withheld until later in the day, when the acute symptoms had subsided, then a dose of castor oil was taken. Following this the acute symptoms disappeared and three days later I resumed work as usual.

On November 13th, I came home at five o'clock in the afternoon, again feeling very uncomfortable. I was tired, somewhat nauseated, yet hungry. I ate an apple and lay down on a couch for a few minutes, and fell

\*Read at the meeting of American Therapeutic Society, Detroit, Michigan, June 20-21, 1930



asleep When I awakened the nausea was more marked I vomited several times I again experienced discomfort in the lower half of the thorax and upper abdomen, similar to that on the previous occasion, feeling as though I were held in a vice The temperature was elevated and the pulse was slow A physician was called, who gave me codein hypodermically to relieve the pain I slept some, but awakened in the night with nausea, vomiting and diarrhea

The situation appeared so serious next morning that I was taken to the hospital Both food and drink were withheld because of fear of a perforated gastric ulcer Temperature was  $101^{\circ}$ , pulse in the fifties, and I appeared severely ill, leucocytes were about 20,000 Aside from the distress previously mentioned an area of hyperalgesia developed about two and one-half inches to the left of the umbilicus, the upper limit being a little above the level of the umbilicus, the lower border being about two and one-half inches below, thoracic cutaneous zones IX to XII fig 1B The area was about two inches wide

The temperature remained elevated to  $100-101^{\circ}$  for about one week Neither food nor water was allowed during the first few days The leucocytes remained high, from 20,000 to 30,000, part of which during the latter period was due to the concentration of the blood due to dehydration from lack of fluid intake The red corpuscles were about 7 000 000 for the same reason. After a week the acute symptoms had subsided sufficiently to permit giving me a barium meal and make a study of the gastrointestinal

canal Before the study was made a probable diagnosis of diverticulitis was made

The x-rays revealed a single diverticulum of the sigmoid, and a marked spasticity of the entire colon above

All symptoms subsided and I left the hospital on the twelfth day After a two weeks' convalescence I returned to work On several occasions during the next six months I had feelings similar to those noticed when the original attack came on, with distress in the lower thoracic and upper abdominal areas These were accompanied by nausea and preceded by a mild constipation The symptoms were promptly relieved by colon irrigations The area of hyperalgesia over the left side of the abdomen, while continuously present except when I would forget it during my busy hours, was always more pronounced during these periods of mild activity

In June 1928, seven months after the initial illness, I was suddenly seized with elevation of temperature, nausea, vomiting, distress in the upper abdomen and lower thoracic areas, and severe diarrhea The diarrhea continued for three days, after which all acute symptoms disappeared except the hyperalgesia, which became very much lessened The relief from acute symptoms lasted for about six months

In December 1928, I was suddenly seized with an acute pain like the stab of a knife, in the lower left quadrant of the abdomen which was accompanied by a cramping of the muscles This passed off and has never since been felt About once in every four or five weeks, from December

1928 to January 1930, some evidence of gastrointestinal symptoms, nausea, discomfort after eating, and constipation appeared

In May of 1929 a very severe diarrhea was brought on apparently from eating some food at a banquet, for others who had eaten of the same food suffered likewise. The diarrhea continued for several days until the diverticulum or diverticuli were apparently emptied of toxic substances, for thereafter marked relief was experienced. Following the diarrhea in May, however, discomfort in the area of hyperalgesia on taking food was often noted, the pain coming on as soon as the food entered the stomach. This was similar to the gastro-colic reflex complained of by many patients, only it was always felt in the area of hyperalgesia.

Before classifying the symptoms manifested during and since the first acute onset I wish to record other symptoms which I had noticed over a period of three or four years prior to the time of the acute attack, and which I, not knowing of the diverticulum, had interpreted as being probably connected with the ureter. On one occasion I had noticed an area of anesthesia over the upper, front and inner aspect of the left thigh in the areas of the 1st and 2d lumbar cutaneous zones, fig 1D, which lasted for a period of two or three days. Another symptom which had been noticed on many occasions during the previous three or four years, and which at times would come on six or eight times a day, was a very acute pain in a small area on the upper inner aspect of the thigh in the 1st lumbar cutaneous zone, and at the

same time in the scrotum in the area supplied by the 3d sacral nerve (fig 1C). This pain would come on suddenly and last only a second or two, but often was repeated several times in quick succession like a series of electric shocks. It was so severe at times that it made me make a sudden audible gasp which would cause those near me to ask what was the matter. This symptom disappeared after the first acute attack and has been noticed only at rare intervals since. These areas are shown in fig 1.

#### THE TOXIC SYNDROME OF DIVERTICULITIS

The toxic syndrome present during the acute attack consisted of most of the usual symptoms which accompany severe toxemia, slight chilliness, cutaneous vasoconstriction, followed by elevation of temperature, tiredness, aching, nervousness, prostration, insomnia, lack of appetite, coated tongue, inhibition of digestion, nausea and vomiting, loss of taste noted when I began to take food, and leucocytosis. Instead of the pulse showing the accustomed rapidity which accompanies toxic states, it was slow. The reflex stimulation through the vagus was able to overcome the central stimulation of the sympathetics, or, possibly some vagotropic substance which acted upon the heart was released from the inflamed diverticulum.

It will be noted that this toxic syndrome, in its peripheral expression produced effects similar to the body's reaction to fear, anger, pain and rage, as described by Cannon, which is expressive of widespread sympathetic stimulation and parasympathetic inhi-

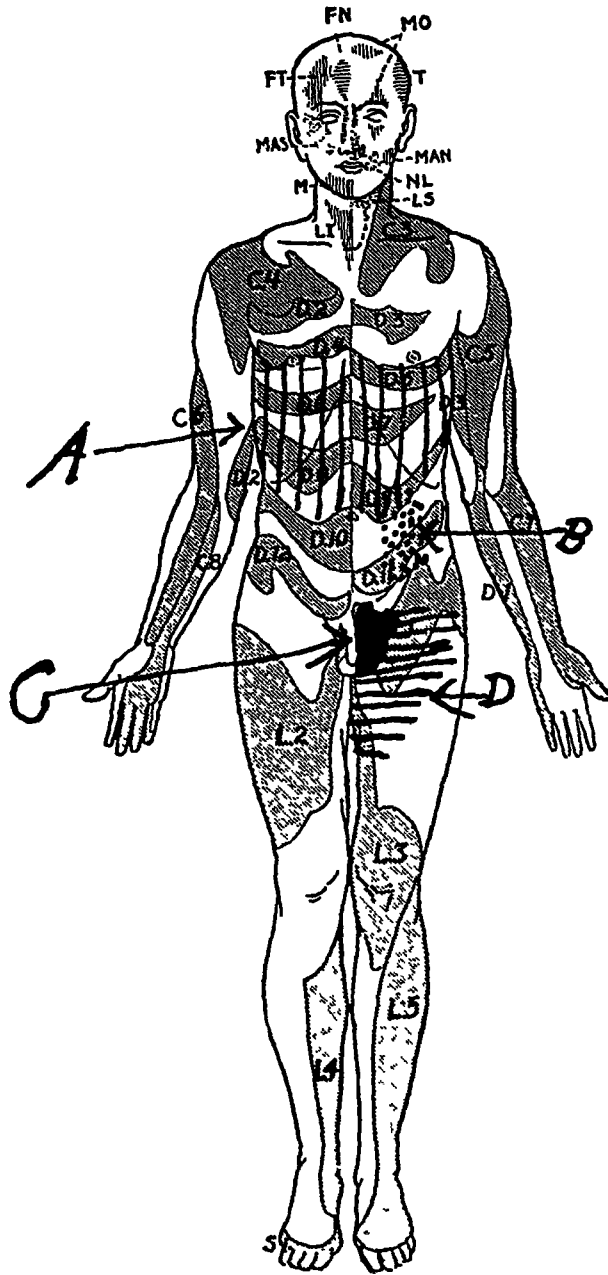


FIG 1 DIAGRAM SHOWING THE LOCALIZATION OF VARIOUS SENSORY PHENOMENA AS EXPRESSED IN HINDS SENSORY ZONES IN A CASE OF DIVERTICULITIS OF THE SIGMOID

- (A) Vertical lines including thoracic zones 5 to 12, area of pain from pylorospasm
- (B) Stippled area sensory zones thoracic, 9 to 12, area of hyperalgesia from diverticulum
- (C) Solid black area in first lumbar and third sacral zones area, in which recurrent pain was experienced
- (D) Horizontal lines in lumbar zones 1 and 2, area in which anesthesia was expressed

bition The effects are expressed in every tissue of the body because the sympathetics are distributed to all, as may be understood from fig 2 The sympathetico-adrenal-thyroid mechan-

ism which speeds up metabolism is stimulated both by the major emotions and by toxemia Any marked toxemia causes prolonged action during which time not only is more than the normal

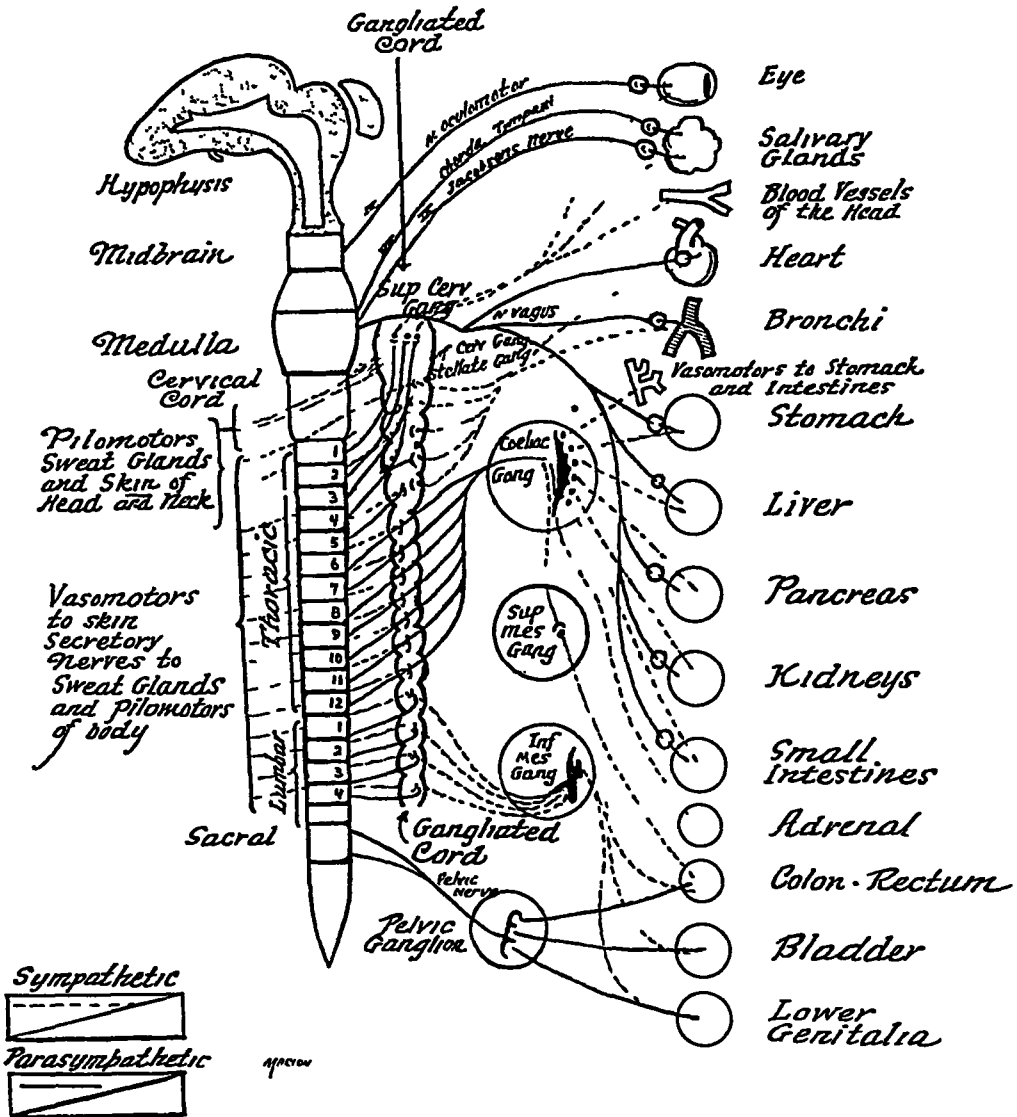


FIG 2 SCHEMATIC ILLUSTRATION OF THE DISTRIBUTION OF THE TWO COMPONENTS OF THE VEGETATIVE NERVOUS SYSTEM, SHOWING ITS DIVISION INTO SYMPATHETIC AND PARASYMPATHETIC AND THEIR BRANCHES TO THE VARIOUS ORGANS

The thoracolumbar portion of the cord, which gives origin to the sympathetic nervous system, is represented by lines. The portions of the midbrain and medulla, and sacral segments of the cord, which give origin to the parasympathetic system, are represented in black. The peripheral nerves belonging to the sympathetics, are shown as solid black lines, while those belonging to the parasympathetics, are shown as broken lines. This chart shows the double innervation of the structures of the head, heart, and the entire enteric system, and likewise indicates the single innervation for the blood vessels, pilomotor muscles and sweat glands of the body (From Symptoms of Visceral Disease)

amount of heat produced but its dissipation is minimized to the point of causing an abnormal heat retention, causing elevation of temperature while the major emotions are of short duration and usually accompanied by sweating and rapid loss of heat. Purely emotional reactions sometimes show an elevation in temperature amounting to a few tenths of a degree but rarely more than a degree.

While the x-rays revealed a single diverticulum filled with barium, and that in the sigmoid, from the study of the pathology and from usual clinical experience in diverticulitis, we are justified in assuming that there was probably more than one.

#### REFLEX SYMPTOMS OF DIVERTICULITIS

Reflex symptoms were evident in the stomach, the colon, the rectum, the heart and in those sensory cutaneous zones which are in reflex connection with the stomach, colon and sigmoid.

The reflex symptoms noticed in this study are many, but can probably best be presented according to the afferent and efferent neurons over which the impulses were carried.

Precedent to the discussion of reflexes which either arise in or are manifested in the gastrointestinal canal, it is necessary to disabuse our minds of any idea that we may possess of the necessity of juxtaposition, in the cord, of the entering and outgoing neurons which form the receptor and effector elements of the reflex arc.

While Sherrington's law that *each afferent neuron finds in the segment of the cord which it enters an efferent neuron with which it will combine most readily in the formation of reflexes*

holds true for visceral reflexes as usually met, it does not preclude combinations of other neurons which belong to different segments of the cord, in the formation of reflexes. Such variation is found in many diseases of viscera. The segments in which reflexes from the important viscera are most apt to occur may be judged from fig. 3, which shows the connector neurons to each of the more important viscera.

It has been shown by Carlson and his coworkers that each and every portion of the gastrointestinal canal may be influenced by irritants applied to each and every other portion of the gastrointestinal canal.

Physiologic evidence points to the possibility of a single afferent impulse being transferred to practically all efferent neurons, as is illustrated in strychnia poisoning, in which a stimulus, whether of sight, sound or touch, may produce generalized spasm of the musculature of the whole body.

Referred pain follows laws similar to true reflexes and bears out the segmental nature of all such effects.

*Response on the Part of the Stomach.* The stomach manifested motor, secretory and sensory reflexes in response to the acute diverticulitis. The effects which predominated were those recognized as being produced when sympathetic action predominates over the parasympathetic. There was nausea, vomiting and a delayed or rather almost complete absence of digestion, for the vomitus ejected at twelve o'clock, six hours after eating, showed the food to be little changed by its residence in the stomach. Eructations of gas were also frequent. We assume,

therefore, that gastric peristalsis was not only deficient but reversed, that the pyloric sphincter was contracted or closed and the cardia relaxed. The distress felt in the thoracic sensory zones Vth to IXth, fig 1A, was bilateral and corresponded to the pain of pylorospasm. Impulses can cross in the cord and produce bilateral reflexes according to well established physiologic laws. This is not uncommon in severe anginal attacks.

If we disregard the possibility of impulses being transferred from one segment of the gastrointestinal tract to another through the nerve plexuses found in its walls, we may account for the transference of the stimuli from the inflamed diverticulum to the stomach by central intersegmental paths. Such stimuli may pass from the inflamed areas in the gut to the cord through the afferent neurons which course with the sympathetics of the

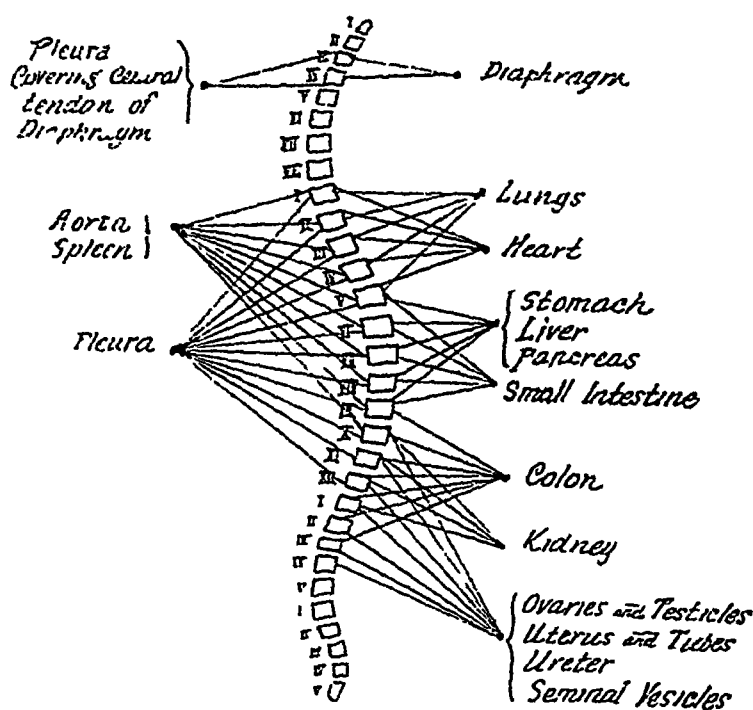


FIG 3 THE CONNECTOR NEURONS FOR THE IMPORTANT THORACIC ABDOMINAL, AND PELVIC VISCERA

In the figure the connecting neurons are those which belong to the thoracolumbar outflow, except those going to the diaphragm, which are spinal nerves (phrenics). The motor cells for the viscera are found in the various collateral ganglia.

The figure shows that the innervation of the various viscera may be divided into groups. The heart and lungs are innervated from practically the same segments, the upper 1st to VIth thoracic. The stomach, liver, pancreas, and small intestine from the same segments, Vth to IXth thoracic. The colon, kidney, and pelvic viscera from practically the same segments, IXth to Xth thoracic to IIIrd and IV lumbar.

This figure shows the colon as receiving innervation from the upper three lumbar segments, as well as the lower four thoracic segments, although this is not generally accepted by physiologists.

In spite of this grouping in innervation, each organ is brought in reflex connection with efferent neurons, both sensory and motor, which are more or less definite, in such a way that the motor and sensory reflexes do not overlap as much as might be indicated. (From Symptoms of Visceral Disease)

lumbar and the lower thoracic segments (in case the lower thoracic segments also supply the colon), whence they may be transferred upward in the cord until brought into reflex connection with the connector neurons (thoracic Vth to IXth) of the sympathetic system, which supply the stomach and pyloric sphincter. The course which such stimuli would follow may be understood from figs 2 and 3.

In this connection it is necessary to inject a few observations on the moot question of the sympathetic and vagus control of the stomach and pylorus. In order to understand the various activities of the stomach it must be understood that peristaltic effects and opening and closure of the pylorus may be carried on autonomously, independent of extrinsic nerves. How efficiently it could be carried on if the intrinsic nerves, as represented by the plexuses of Auerbach and Meissner were removed, is a question. At the same time we must recognize that smooth muscle, regardless of nervous effects, possesses the property of tonus and rhythmic action.

The question of the control of the pylorus has not been definitely established by experiment. It seems certain from experiments from Carlson's laboratory that both sympathetic and vagal stimulation are able to cause its closure. Nevertheless, reasoning from analogy, in case of other sphincters, the innervation of which is not disputed, we must ascribe to the sympathetic nerves the preponderance of activating control, and to the vagus an inhibiting action for both the sphincter and the antrum.

It seems but natural that every organ whose exit is guarded by a sphincter should possess a nervous mechanism so arranged that a stimulus which closes the sphincter will at the same time relax the musculature of the body of the organ, and that a stimulus which relaxes the sphincter will at the same time increase the tension of the muscle of the body of the organ, so as to aid in its emptying, as is found in the urinary bladder. This reciprocal innervation, according to the idea of Meltzer, seems essential to physiologic efficiency of action.

There is also considerable discussion as to the exact part played by the sympathetic nerves in the innervation of the fundus, cardiac sphincter and esophagus. It seems that the sympathetic nerves are represented by few fibers in these structures; in fact, some authors claim that the entire nerve control, both activating and inhibiting, depends upon the vagus, and that contraction and relaxation is due to stimulation of different fibers of the nerve. It is at least safe to say that a preponderance of vagus control is proved for the cardiac sphincter and esophagus, and that possibly the same is true for the fundus, although the sympathetic fibers that are present probably aid in producing inhibitory effects.

During the acute phase of the diverticulitis, if the aforementioned innervation is correct, gastric and pyloric effects were noticed which may be explained as representing a preponderance of sympathetic stimulation while the effects in the cardiac sphincter and the structures on both sides of it represented vagal inhibition.

probably largely due to the stimulation of vagal inhibitory fibers. Such were pylorospasm, relaxed cardia, cessation of peristalsis and secretion, dilatation of the fundus and esophagus, and the reversed peristalsis associated with vomiting. It is not entirely clear how these effects were produced. The stimuli may have arisen in either the diverticulum or stomach. If they were caused reflexly by the diverticulum, the stimulus must have been transferred to intrasegmental paths in the cord either through the afferent fibers of the sympathetic system or through the sacral nerves of the parasympathetic system. But no matter over which system the afferent impulses were transferred, on entering the cord the stimuli must have been carried upward to some central cerebral station from which they were distributed. It is assumed, however, that the parasympathetics usually carry the visceral afferent impulses which cause vomiting.

It is further possible that some or even all of the impulses which caused the vomiting might have arisen in the stomach itself, for the pylorus was closed, the musculature of the antrum was probably contracted, the fundus, cardia, and the lower portion of the esophagus were relaxed, and the food was not digested, therefore, it was natural that the stomach should have attempted to empty itself.

The act of vomiting is released from some common nerve station in the brain, probably in the medulla from which stimuli must be sent out to produce three distinct effects which are necessary to accomplish it as follows: (1) efferent impulses must be

sent over the sympathetics to the pylorus and pyloric end of the stomach, contracting them, and opposing vagal action in all areas innervated by both systems resulting in inhibition of peristaltic action and gastric secretion; (2) over the inhibitory fibers of the vagus to the cardiac sphincter, the fundus of the stomach and the lower portion of the esophagus, supplementing the antagonistic action of the sympathetics and relaxing them, the total nerve effect being to check and reverse the peristaltic waves, and (3) over skeletal nerves to the diaphragm and the abdominal muscles, causing them to contract and expel the contents from the stomach. The mechanism of emptying would be the same whether the stimuli arose in the stomach itself or in the inflamed diverticulum, or in both the stomach and the diverticulum.

The vomiting mechanism may be stimulated to activity by all kinds of sensory disturbances—sight, smell, sound, touch, intracranial pressure; or sensory impulses from various organs, such as the eye, heart, lungs, stomach itself, liver and gall-bladder, pancreas, or any other portion of the gastrointestinal canal, the kidney, bladder and the genital organs, or by psychical impulses, such as fear, disgust, worry, pain and so forth.

*Response in other Parts of the Intestinal Tract* According to the law of the intestine, when a stimulus is applied to any portion of the gastrointestinal tract the motility of that portion of the gastrointestinal tract above the stimulus is slowed and that below is increased. True to this law hyperactivity beyond the point of inflamma-



tion was shown by the diarrhea. Inhibition of activity above the point of irritation was shown in the stomach as above mentioned, and we assume that the same inhibition was probably present in the small intestine. In the colon it was shown by a persistent tendency to constipation after the acute attacks were over, something that had never shown before.

### *Reflexes in the Skeletal Structures*

Several different reflexes were noted in the skeletal structures, most of which were of a sensory nature, if I may be permitted to speak of the referred pain, the hyperalgesia and other sensory phenomena as though they were reflexes. Motor and trophic phenomena were also present.

The phenomena described above in connection with the stomach were only partly directly due to the diverticulitis. The stomach was so thoroughly thrown off its normal course of action, that we may assume that a local condition might well have been set up in it which was accompanied by symptoms which almost dominated the picture.

The muscles on the left half of the abdomen, in the area marked by the hyperalgesia, fig. 1B, showed a *motor reflex* during the acuteness of the attack and at one time, as previously mentioned, there was a spasm of the muscles in the lower left quadrant which was so severe that I was obliged to stop my work for a few minutes. In this connection, it must be borne in mind that broad muscles contract reflexly in segments and not as a whole. In this they differ from the long muscles of the extremities.

The persistence of the hyperalgesia was indicative of marked and prob-

ably permanent injury to the neurons, if we may judge from the fact that it still persists more than two and one-half years after its beginning. Any stimulation continuing over such a period of time would be expected to cause permanent effects in the way of *trophic reflexes*. These are recognized as an atrophy of the skin, subcutaneous tissue and muscles in an area coextensive with the area of hyperalgesia, fig. 1B. The tissues here have lost their normal texture and give an impression of loss of elasticity and firmness, similar to the trophic reflexes which I have described in the dermal tissues which receive stimuli from the lung over a long period of time, as seen to best advantage in chronic pulmonary tuberculosis.

*Sensory Reflexes* The sensory impulses which were referred to different skin areas require special consideration.

The thoracic localization of hyperalgesia in the IXth to XIIth thoracic segments is irregular for sigmoid involvement, if the sympathetic innervation is, as usually given, from the lumbar segments through the inferior mesenteric ganglion. Nevertheless, the most constant and most evident sensory phenomenon experienced by me from the time of the appearance of the first symptom of active disease until the present time has been the hyperalgesia in these sensory zones to the left of the umbilicus.

In accounting for the localization of hyperalgesia, three possibilities must be considered. (1) Assuming that the entire colon receives its innervation through the inferior mesenteric ganglion from the lumbar segments alone,

which is in accordance with the teachings of most physiologists, we must account for the hyperalgesia in the IXth to XIIth thoracic segments by the transference of the impulses from the sigmoid upward in the cord, through intrasegmental paths (2) Assuming that the colon receives innervation through both the superior mesenteric ganglion from the lower thoracic segments, and the inferior mesenteric ganglion from the lumbar segments, which is in accordance with the teachings of some physiologists, and which is followed in the illustration (fig 3) which shows the connecting neurons for the important viscera, then the area of hyperalgesia could be caused perfectly regularly by inflammation in the sigmoid, according to the usual law which governs segmental reflexes (3) Assuming that the small intestine is innervated through the superior mesenteric ganglion from the lower thoracic segments only, and that the large intestine receives innervation through the inferior mesenteric ganglion from the lumbar segments only, then, if the area of hyperalgesia was produced regularly according to the law which governs segmental reflexes, it would be necessary for the lesion causing the hyperalgesia to be in the small intestine There was no evidence of this found, however, on physical and x-ray examination

This is the only clinical observation connected with the case that offers particular difficulty in explanation on the basis of the sigmoid receiving its sympathetic innervation alone from the lumbar segments of the cord

The area of anesthesia in the upper inner aspects of the left thigh in front, in the areas supplied by the Ist, IIId and IIIId lumbar (fig 1D) nerves, and the acute pains in the area supplied by the first lumbar nerve, together with the scrotal pain in the areas supplied by the IIIId sacral nerve were perfectly regular in their localization if the sigmoid is innervated by the lumbar segments alone These pains, strange to say, almost totally disappeared after the second acute attack of inflammation in June of 1928

The area of hyperalgesia has been most interesting because of its localization, its varying quality, and its constancy It always has been present when I have looked for it It was not noticed previously to the acute attack of November 1927 It lessened for a time after the acute attack in June 1928, to return fully a little later At times it was so pronounced that I would find myself lifting my clothes off it, for their pressure was sufficient to cause discomfort

*Reflex from Stomach to Diverticulum* A very interesting phenomenon which appeared months after the acute onset was what might be called a reversed reflex from the stomach to the diverticulum Just as I had a reflex stimulus from the inflamed area to the stomach and pylorus causing the pain of pylorospasm in the thoracic sensory zones Vth to IXth, so I noticed at certain periods that when food was taken into the stomach there was an increase in the sensation in the area of hyperalgesia This symptom did not come on during the first year It was possibly connected in some way with the chronic irritation of the neurons

The stimulus must have been conveyed downward in the cord from the gastric neurons to those connected with the sigmoid. It is probably the same type of abdominal distress as is so often complained of when patients who have had irritative lesions in the gastrointestinal tract take food into the stomach.

#### THE CAUSE OF RECURRENT SENSORY PHENOMENA (PAIN)

After my own experience I can well understand those complaints of recurrent pain or discomfort on the part of patients who have previously suffered from inflammation of some abdominal viscus, although no definite symptoms of active disease can be elicited at the time. I am sure if I had not been a student of visceral neurology that I would have urged and probably forced my surgeon to operate to relieve me, particularly because the discomfort always recurred in the same place, in the area of hyperalgesia. Then later, when it again manifested itself, following eating, this would have had a tendency to remove all doubt and make certain that there must be some serious trouble which probably called for operative procedure.

As physicians, we do not sufficiently appreciate the fact that whenever a viscus has been chronically inflamed, recurrent sensory disturbances may appear in the areas on the surface of the body to which pain from that viscus is referred, without there being present any active inflammatory process at the time. These referred sensory disturbances on the surface of the body are usually accepted as meaning

active disease of internal viscera when in reality they very often mean instead that the threshold of response on the part of the sensory neurons has been lowered somewhere in the pathway from the viscus to the area of expression on the surface of the body, or to the areas of consciousness in the cerebrum, rendering the transference of sensory phenomena abnormally easy.

There is the same connection between afferent nerves and the sensory nerves on the surface of the body during conditions of visceral health that exists in conditions of visceral disease; but it is only in conditions of disease that sensation or pain is manifested, because under normal conditions the threshold of reaction in the sensory paths and the central inhibition by which normal stimuli are prevented from reaching consciousness and are held to their vegetative levels, are both normal, but when, through disease of some internal viscus, afferent impulses have been repeatedly carried centralward, over a long period of time, the sensory mechanism becomes hypersensitive so that impulses are transmitted more readily than under normal conditions; and the central inhibition is broken down so that the irritation which is responsible for the pain or discomfort registers in the brain, although it is a lesser stimulus than that which would be necessary to overcome the threshold of response and register in the brain if the sensory mechanism had not been previously injured.

This situation is met frequently in our practice, but usually goes unrecognized. A patient who has had such

diseases as tuberculosis, pleurisy, inflammation of the gastrointestinal tract, inflammation of some pelvic viscus, arthritis or neuritis, suffers from recurrent pain under many conditions of stress, such as acute or chronic fatigue, worry, discontent, unhappiness, ill health, at the time of menstruation, and with changes in weather or seasons, which are in no way directly related to the diseased viscus. These, however, are all conditions which call for considerable physiologic adjustment, and the neurons injured by preceding disease fail to make the adjustment and so show pain or discomfort.

*Reflex in Heart* The bradycardia noted, unless due to chemical stimulation as mentioned above, was a reflex through the vagus, the impulse being transferred to it in the medulla by intersegmental nerves which picked up the stimuli in the lower segments of the cord and carried them upward from either the sacral or from the lower thoracic and upper lumbar sympathetic nerves. Reflex bradycardia is not infrequently found in tuberculosis, in gastric ulcer and in infections of the bowel, liver and gall bladder.

#### SUMMARY

1 An attempt is made to explain in terms of vegetative neurology the major symptoms personally experienced in recurrent attacks of diverticulitis.

2 I have attempted to show by this analysis how the vegetative nervous system integrates and correlates action in different parts of the body, and how the normally submerged reflexes which are present but not in the field of consciousness in conditions of

health may disturb function and produce symptoms when they are exaggerated by the inflammatory process of disease.

3 The various reflexes and referred sensory changes which manifested themselves during the illness are described and as far as possible ascribed to the afferent and efferent neurons which were responsible for their production.

4 The method by which a chronically inflamed viscus may produce recurrent pain when no active inflammation is present is discussed in connection with the subject of recurrent sensory phenomena. It is pointed out that whenever a viscus is chronically inflamed there is more or less permanent injury produced in the path of sensory expression leading from that viscus, as a result of which pain or other sensory phenomena are thereafter produced upon a minimum of irritation. Such sensations are apt to occur whenever an extra amount of strain is thrown on the patient's physiologic adaptive mechanism. They come with tiring, worry, other illness, seasonal changes, changes in weather, and in women they are often associated with the menstrual period.

5 The reflex in the hyperalgesic area noticed on taking of food explains the complaints of patients which are met so often when there is some inflammatory reaction in the intestinal tract, such as appendicitis, ulcer of stomach or intestine, and tuberculosis of the bowel. As soon as food enters the stomach pain is felt in the area in which it is referred from the inflamed organ.

# Treatment of Septic Meningitis by Intra-Carotid Serum Therapy\*†

## Report of Two Cases of Pneumococcus Meningitis and One of Meningococcus Meningitis

By JAMES A. EVANS, A B, M D, F A C P, *La Crosse, Wis.*, and  
SYLVESTER N. WELSH, M D, *Chicago, Ill*

IN THE treatment of any form of meningitis it is of utmost importance to bring our medication in as great a concentration and as close proximity as possible to the greatest area of disease. Intra-spinal was the first improvement over intravenous therapy in this direction and combined with the latter is often successful in the treatment of meningococcus meningitis. The next step was intra-cisternal injections<sup>1</sup>, then intra-ventricular, and finally intra-arachnoid injections together with various combinations of these methods. All of these procedures often fail when plastic exudates have caused sub-arachnoid blocks.

Hirsch, Myerson and Halloran<sup>2</sup> first used intra-carotid injections of arsenicals in the treatment of general paresis. Kolmer<sup>3</sup>, et al, following this lead, injected pneumococcus serum and numoquin-base into the carotid arteries of dogs in which they had induced pneumococcus meningitis. They

attained 66% cures in these dogs after disappointing results in curing control animals of experimental pneumococcus Type I meningitis by combined intra-carotid, intra-cisternal and intra-spinal injections of anti-pneumococcus serum and numoquin-base.

It is most important to deliver our antibodies to the cerebral and basal meninges in as great concentration as possible. Lumbar intra-theclal India ink injections in cadavers have been found by Ayers<sup>1</sup> to diffuse higher than the cervical region only to a very limited extent. Intra-cisternal injections enable the India ink to reach the basal and cerebral cortical meninges. However, Kolmer<sup>4</sup> found that many of his failures to cure experimental septic meningitis by cerebral sub-arachnoid injections were due to remaining foci of plastic meningitis over the cerebral meninges. Therefore, even sub-arachnoid injections often fail to eradicate the disease here because of plastic exudates blocking the diffusion of antibody solutions over the surface of the cerebral hemispheres. Intra-carotid injections allow the serum to be brought to the cerebral meninges directly with a minimum of dilution and

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†From the Extra-Mural Preceptorial Medical Service of the University of Wis., St. Francis Hospital, La Crosse, Wisconsin.

sub-arachnoid blocks can have no effect in inhibiting its diffusion Kolmer<sup>3</sup> states that precipitin tests after intra-carotid injections of antibody serum into normal animals have proved the presence of antibodies in the spinal fluid Some of the serum is certainly lost through the external carotid artery, but this being the smaller branch, the loss is comparatively unimportant

As suggested by Kolmer, we have tried the combined intra-carotid, intra-cisternal and intra-spinous injections of Huntoon's antibody solution plus ethylhydrocuprein base together with cisternal and spinal drainage in two cases of pneumococcus meningitis with failure The first of these two cases, a girl of eighteen, had a stiff neck and vomiting for two days before entering the hospital Fifteen cubic centimeters of turbid spinal fluid under great pressure containing 1,250 pus cells per cubic millimeter were replaced by ten cubic centimeters of anti-meningococcus serum A smear stained immediately by Gram's method showed Gram positive encapsulated pneumococci, confirmed by culture The next morning, the third of her illness, both carotid arteries were exposed under light ethylene anesthesia and twenty cubic centimeters of a mixture of Huntoon's pneumococcus antibody solution and five cubic centimeters of 1% numoquin-base were injected into each artery through a small gauge hypodermic needle Immediately after, a cisterna magna puncture was made, eight cubic centimeters of bloody spinal fluid were withdrawn, and replaced by ten cubic centimeters of the same mixture as above There was no untoward reaction but five hours later the patient

died very suddenly from what seemed clinically a cerebral embolism

The second fatal case of pneumococcus meningitis was secondary to a long debilitating illness with measles, otitis media and mastoiditis in a girl of seven The only meningeal symptom was gradually increasing stupor, but no clinical signs of meningitis developed before treatment for meningitis was instituted Meningitis was first suspected on the forty-second day of illness when lumbar puncture yielded six cubic centimeters of cloudy spinal fluid under increased pressure containing 260 lymphocytes and 1,000 pus cells The smear stained by Gram's method showed Gram positive diplococci present In the next four days six intravenous injections of forty to fifty cubic centimeters of Huntoon's pneumococcus antibody solution were administered Five spinal drainages and five simultaneous intra-spinal injections of four to ten cubic centimeters of Huntoon's solution plus 1% numoquin-base were given in the same four days During these days the temperature had dropped from a daily height of 104° to 102° and the pulse from 150 to 90 On the sixth day the spinal fluid still being cloudy and definite meningeal signs having now developed desperate measures were considered justified Under ethylene anesthesia both carotid arteries were exposed and eleven cubic centimeters of Huntoon's pneumococcus antibody solution plus five cubic centimeters of 1% numoquin-base were injected into each carotid artery The cisterna magna was immediately drained of ten cubic centimeters of cloudy fluid and six cubic centimeters of the antibody solu-

tion plus one cubic centimeter of 1% numoquin-base injected. The patient never recovered consciousness and died seven hours later. The culture showed a mixed streptococcus viridans infection.

Following these two failures an apparently fulminating case of meningococcus meningitis presented itself in which coma had developed within twelve hours of the first signs of meningitis. It seemed advisable to us to try to reach the cerebral and basal meninges with antiserum in such a case as thoroughly as possible.

**Case Report** A farmer of forty-two was admitted to the hospital February 19, 1930, unconscious. Three days before he had caught cold. On the morning of the third day he had a terrific headache and the same evening became unconscious. On admission the temperature was 102°, pulse 88, respiration 20, and white blood count 24,250. The

pupils were regular, equal and reacted to light. There was haziness of both optic discs, a purulent discharge from both nostrils, congested pharynx and herpes about the mouth. The neck was very rigid. The knee jerks were exaggerated bilaterally, ankle clonus was present on both sides with bilateral positive Babinski together with positive confirmatory Oppenheim and Gordon signs. Kernig's sign was elicited bilaterally. Spinal fluid on entrance was cloudy with a cell count of 12,000, about 80% of which were pus cells. Gram positive diplococci were seen in the smear. The culture was reported positive for meningococci. Fifteen cubic centimeters of antimeningococcus serum were given intraspinally at the same tap. For the next three days a daily intra-carotid injection of antimeningococcus serum was given, combined with cisterna puncture and serum injections. Both arteries were exposed in the neck, no anesthesia being required the first day, and under light gas anesthesia on the second and third days. Five cubic centimeters of antimeningococcus serum were in-

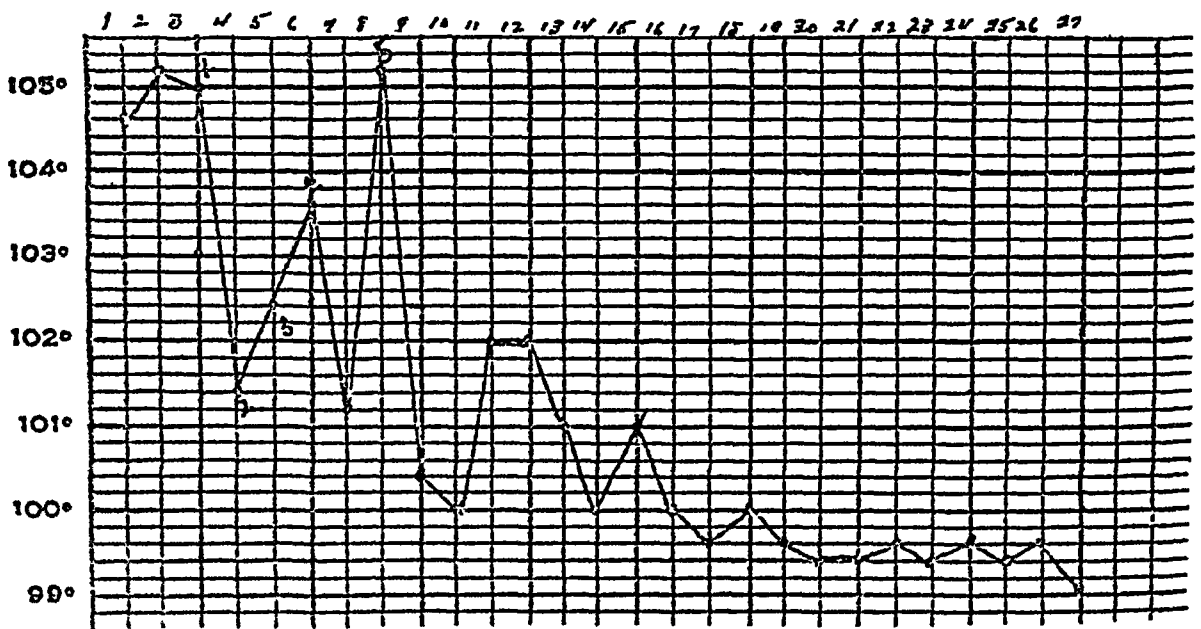


CHART 1. Condensed temperature chart giving highest temperature each day. Points 1, 2 and 3 indicate intra-carotid and cisterna magna medication. Point 5 indicates highest temperature reached during serum sickness.

Antimeningococcus serum was given intraspinally daily the first seven days in the hospital, then every other day for the next ten days, then every third day for the next nine days. Last injection after lapse of one week.

In all 350 cc of antimeningococcus serum were given by various routes.

TABLE I CEREBRAL SPINAL FLUID EXAMINATION OF A CASE OF MENINGOCOCCIC MENINGITIS—(LUMBAR PUNCTURE)

Date	Pressure	Character	Cells	Globulin	Collodial		Wass	Culture	Smear
					Gold	Curve			
2-18-30	Increased	Cloudy	12,000	Positive	0000112321		Neg	Positive	Positive
2-20-30	Increased	Cloudy	8,000	Positive				Positive	Positive
2-22-30	Normal	Translucent	2,750	Positive	0000012332		Neg.	Positive	Positive
2-25-30	Normal	Translucent	5,280	Positive			Neg	Positive	Negative
2-27-30	Normal	Translucent	2,120	Positive	0000012332		Neg	Positive	Negative
3- 1-30	Normal	Transparent	1,620						
3- 6-30	Normal	Fairly clear	340						
3-13-30	Normal	Clear	130	Positive	0000012332		Neg	Negative	Negative

\*A clear jelly-like clot formed on standing fifteen minutes

jected slowly into each common carotid artery with a small hypodermic needle. There was no bleeding following withdrawal of the needle though on one occasion a small hematoma formed in the wall of the vessel. Ten cubic centimeters of turbid spinal fluid were withdrawn from, and ten cubic centimeters of antimeningococcus serum were injected into, the cisterna magna at each cisternal puncture. The first two days he also received serum intravenously and intraspinaly.

The evening following the first intra-carotid and intra-cisterna magna treatment the patient recovered consciousness. He received ten to twenty cubic centimeters of antimeningococcus serum intraspinaly daily for the first two weeks in the hospital. Convalescence continued uneventfully except for a serum reaction on the eighth day when the temperature rose to 103.8°. The chart and table appended show the detailed progress of the case. The smear became negative for organisms in one week but the culture was not reported negative until the twenty-third day. We discharged him on the twenty-eighth day apparently recovered. When last heard from seven months later the patient was well. His home doctor reported that he started work one month after discharge from the hospital and that for four months he was quite deaf.

### CONCLUSIONS

1 On theoretical and experimental grounds intra-carotid combined with intra-cisternal serum therapy would seem the most efficacious method in treating an infectious process in the cerebral meninges.

2 Two cases of pneumococcus meningitis were treated unsuccessfully by this method.

3 A very fulminating case of meningococcus meningitis was treated successfully, the patient regaining consciousness eight hours after the first treatment.



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# Delayed Organic Diseases of the Nervous System Following Traumatism and the Question of Appraisal of Disability for Compensation\*

By ALFRED GORDON, *Philadelphia*

IN traumatic affections of the nervous system two possibilities are considered one when they follow the accident immediately and consist of a damage to the cellular tissue or to the projection and association tracts with the result of immediate cessation of function of the parts depending on those nervous elements. The other possibility is when a certain more or less considerable interval passes between the date of the accident and the appearance of the disturbed function in the body. The first occurrence does not require any special emphasis, as the relation between the trauma and sensorimotor manifestations is very evident. It is the latter that is more important and it is to it that the present contribution devotes some analysis and consideration.

That an organic disorder of the nervous system does develop some time after a trauma, all neuro-clinicians have recognized, and it is now well established. As an example of it we find the so-called "Spatapoplexie" in

which the symptoms appear ordinarily within two to eight days after the trauma. If, however, the clinical symptoms make their appearance only two or three weeks after the accident, as a rule the latter is no more incriminated and other etiological factors are sought after, such as cardio-vascular diseases, tumor, etc. In the series of cases presented here six developed symptoms of organic nature shortly but not immediately after the trauma, four cases began to show symptoms a long or a very long time following accidents.

GROUP I *Case A* D G., laborer, 35 years old, was hit by an automobile. In falling the head struck a stone wall. He was unconscious for five hours. Roentgenography revealed no fracture of the skull or of any other bony structure. A small hematoma over the left temporal region was noticeable. The patient improved greatly so that on the fifth day he left his bed. On the sixth day after the accident it was observed that the patient had to raise his head in order to be able to see objects in front of him. Close examination revealed ptosis on the left side, palsy of both superior recti muscles and of the left internal rectus. There was evidently an apoplectic damage irregularly distributed in the midbrain at the level of the nuclei of the third nerve on both sides. Except for a slight improvement, the af-

\*Read at the June meeting of the American Neurological Association in Atlantic City

fectured ocular muscles remained unaltered ten months later. Repeated tests of the blood and the spinal fluid revealed no reaction suggestive of lues. The patient however complained of persistent headache.

*Case B* A S, man of 40, clerk, was attacked and hit over the right temporal region with a hammer. He fell dazed, bleeding was noticed from the injured scalp area. However x-ray revealed no fracture of the skull. He made apparently an uneventful local recovery and resumed his occupation. Three weeks later he came complaining of a slight headache and occasional twitching of the left upper lip. A close examination revealed a slight lowering of the lower portion of the left side of the face and a decided weakness of the grip of the left hand. The muscular twitching of the lip became more and more frequent. Next he was seen one year later and his former condition remained unaltered.

*Case C* O N, laborer, 23 years of age, suffering from mental depression, in an attempt at suicide jumped from the roof of his two story house down on the pavement. He sustained a fracture of one tibia but the skull was intact. He was unconscious for two hours. Five weeks later while in bed he developed a weakness of the right arm and a mild disturbance of speech articulation. The condition of the arm persisted, but the speech disorder would disappear and reappear and last but a fraction of a minute. The patient was seen two years later. The paresis of the arm persisted, and the speech became decidedly defective.

*Case D* K. P, male, a roofer, 32 years old, heretofore physically and mentally sound, accidentally fell down while at work. He was semiconscious when picked up. One arm was fractured. X-ray showed the skull intact. The general condition was good on the next day. The humerus was set and he was able to walk around his room. He ate and slept well. On the sixth day he noticed that saliva would run out of his mouth on the right side and his speech became indistinct. Examination revealed a mild facial paresis of cerebral type, a slight weakness of his right hand and distinct astereognosis in the same hand. The patient was seen six

months later and the above condition was found unaltered.

*Case E* E R, dressmaker, 37 years of age, in getting off a railroad train, tripped and fell striking the head against the platform. She was unconscious for 4 hours. X-ray failed to reveal a fracture of the skull. She was confined to bed 48 hours. There was a complete amnesia of the accident and she never recovered her memory for the event. On the 3rd day she left her bed and resumed her house duties and her dressmaking work. Three days later, that is on the sixth day after the accident she became vertiginous and fell. There was no unconsciousness. A right mild hemiplegia with anarthria was observed. One year later she presented the same parietic condition of her limbs, but the speech became normal.

*Case F* R N, female, 54 years of age, very obese, having a history of chronic articular rheumatism since the age of 36, presenting also some deformities with enlargement of the small joints of her hands, fell accidentally from a flight of stairs. The right humerus was fractured. There was no loss of consciousness. After the preliminary shock, an orthopedic apparatus was placed on her arm. She was in bed but four days. On the seventh day she began to complain of paresthesiae and occasional lancinating pain in the lower extremities. She never experienced this disorder prior to the accident. Gradually she observed that her gait was becoming altered. She could not go upstairs without considerable support. She scraped the floor in walking. Examination revealed increased knee-jerks, some resistance to passive movements, a slight bilateral ankle-clonus, extensor plantar reflex on the left and no response on the right side. Objective sensibility was only diminished. The sphincters were not involved. She was seen again 16 months later. There was a typical spastic paraplegia with all the characteristic reflexes.

*Group II Case A* S N, male, 16 years old, was struck on the head by bricks which fell from a building in construction. There was a scalp wound over the left parietal region. No loss of consciousness. During six months the boy felt perfectly well. Then he commenced to experience an occasional

headache and have attacks of vertigo accompanied by diplopia, of a two minutes' duration. Soon he complained of occasional twitching of the right angle of the mouth and of a tingling sensation in the right arm. These attacks became more frequent. Objective examination revealed a paretic condition of the right arm and astereognosis of the hand on the same side. The patient contracted pneumonia and died nine months after the accident. A postmortem showed adhesion of the meninges to the cortex over the middle third of the ascending parietal convolution.

*Case B* A N, sailor, 30 years of age, heretofore in perfect health, fell down a ladder on his ship. His head struck the floor violently. He was unconscious for 10 minutes. In the evening of the same day he resumed his work. On the next day he had a vomiting spell followed by a generalized convulsive seizure. He promptly recovered. During the next seven months there was no recurrence of the attacks, but very occasionally he would complain of frontal headache. The latter would last but a half-an-hour and occur only on damp days. He worked steadily, never complaining. Eight months after the accident the headache became more frequent. Vertigo set in. He complained of attacks of diplopia. Suddenly he would lose the power in his left arm and leg and then recover it. Gradually an actual paretic condition developed in both limbs on the same side. Convulsions soon made their appearance. They were confined to the left side. The fundi showed then optic neuritis. The diagnostic presumption was at that time strongly in favor of a right-sided cerebral neoplasm. It was verified on the operating table.

*Case C* R S, female, 35 years old, was attacked one evening on the street and in the struggle was thrown against a stone wall. She fell unconscious. Two hours later she recovered. After remaining in bed several days, she resumed her house duties. For 3 months there was absolutely no inconvenience whatsoever. Then only she commenced to complain of "lapses of memory," as she called it. They were attacks of petit mal. Gradually they became quite frequent. Objects would fall out of her hands, or she

would suddenly become silent while conversing, or she would wander off. In the fifth month after the accident she developed a severe headache with attacks of vomiting. Objective examination showed a paretic condition of the right arm and leg with all the pathological reflexes characteristic of a left-sided lesion in the brain. Papilloedema was discovered in both eyes. A diagnosis of a cerebral neoplasm was made. The patient refused an operation. She died in the eighth month after the accident. Autopsy was not permitted.

*Case D* W W, male, 19 years old, met with an accident in a collision of two automobiles. Sitting at the wheel he was thrown against the windshield which was broken. A fragment of the glass made a cut on the right side of his forehead. The bleeding was profuse. X-ray revealed a linear fracture on the same side. The wound healed up and the patient recovered from the shock. During 11 months there was no indication of any disorder. The patient appeared to be in excellent health. Soon he began to call attention to a weakness of the left hand and occasional twitchings in the fingers of the same hand. This was soon followed by an extension of the clonic contractions to the entire left arm. The paretic condition became deeper and complete paralysis set in. Examination revealed also a decided drooping of the lower half of the left side of the face. Each attack would commence and terminate abruptly. There was no loss of consciousness. The patient developed severe headache at the level of the old scalp scar. The diagnosis of Jacksonian epilepsy was made and in view of the old trauma the lesion was supposed to be either an exostosis of the right frontal bone or a cicatrix involving the cortex and adherent meninges or both. An operation revealed old cicatricial tissue in the middle portion of the right motor convolution. Patient was seen again two years after the operation. He still has occasional headache and at intervals a convulsive attack in the left arm.

To sum up the two groups of cases, we find that the delay of development of organic symptoms referable to the

central nervous system was in the first series from six days to five weeks, while in the second series from six to eleven months. A very important observation was made during the entire duration of all the patients' illnesses. As a routine measure every patient was examined from every angle with the object of determining whether or not the organic neurological manifestations were the result of a preexisting luetic infection or of some constitutional disease rather than of the direct material damage done to the tissue by the trauma. All laboratory tests were done repeatedly and a careful search of previous medical histories was undertaken. The results being entirely and invariably negative, the trauma alone was incriminated. In some cases either the operative field or postmortem verified the contention. In other cases the clear and distinct course of events chronologically following each other also indicated the direct etiological relationship. In the entire series of these cases the epithet "traumatic" was undeniably justified. All imaginable precautions were taken to ascertain the authenticity of the statements of the patients themselves, of their relatives and of the personalities who have no direct or indirect interest in the outcome of the cases under discussion.

The subject of slightly or much delayed onset of symptoms indicating a serious material damage of the nervous tissue acquires thus a grave importance, first from the scientific standpoint, next from the social point of view. In the former it is well to take a firm stand in favor of the position that cicatrices found in the operating field in the meninges or in the cerebral tissue itself, or

else other formations, may all undoubtedly be the result of an old or of a very old traumatic injury. Frequently a persistent and painstaking analysis of the patient's medical history will not fail to reveal a series of slight or very slight ("petits signes" of the French authors) manifestations which do not incommode the patient and do not interfere with his daily activities for a long time from the date of the accident. At this juncture it is well to recall the work of W. Penfield in *Brain* 50:499, 1927 and Penfield and R. C. Buckley in *Arch. Neurol. and Psych.* 20:1 (July) 1928, also and particularly the contribution of E. A. Linell (submitted for publication on Aug. 31, 1928 in the *Arch. Neurol. and Psych.* p. 927). The latter found following cerebral trauma histologic changes in the connective tissue, especially in the microglia, macroglia and astrocyte cells of the nerve tissue. Reactive signs can be seen in both types of cells as early as the third day following the injury. The activity of the microglia reaction is that of scavenging the damaged brain tissue and particularly in removing the myelin of the damaged medullary sheaths. This activity reaches a maximum within a comparatively few days after the injury and is far advanced by the time the wound is three weeks old. The macroglia and astrocyte cells show a maximum reaction of three weeks; the astrocytes play an important and permanent part in the mechanism of wound repair, namely in the formation of a protective brain cicatrix. The same author has thus traced injuries of between three and sixty-two days.

The studies of concussion of the brain also present very interesting pathogenetic elements for an analysis of traumata followed by delayed manifestations of organic nature. While formerly the mechanism of traumatic lesions of the brain was considered as due to a derangement of the molecules of the brain (Bauchet *Des lésions traumatiques de l'encéphale*, 1860), now we have evidences of the presence of multiple punctate hemorrhages in cases of concussion (Cassasa *Proc N Y Pathol Soc* 1924, p 101, Onato and Giliberti *Arch Neurol and Psych* 1927, p 181). We have no more right to consider concussion as a transient state without a structural damage but, on the contrary, we may expect late degenerative changes. Martland and Beling have suggested the term "concussion hemorrhages" (*Arch of Neurol and Psych* Nov 6, 1928). They observed this condition even in the absence of fracture of the skull. These hemorrhages are minute but multiple, diffuse and most frequently met with in the basal ganglia. Their mechanism finds its best explanation in Cassasa's views. During a concussion there is a sudden overfilling of the perivascular spaces with cerebrospinal fluid which is driven in by pressure caused by the change of shape of the skull and which thus lacerates bloodvessels by tearing off their walls from their attachments.

The pathological conditions just considered, namely the sudden hemorrhages (though minitary in size) and the rapid changes developing in the neuroglia even as early as the third day after trauma—are both sufficient to view every head injury, however trivial, from a serious standpoint and always

bear in mind the possibility of delayed development of an irreparable degenerative alteration in the most important elements of the nervous system. This information leads to the consideration of the second or social part of our study, namely the appraisal of disabilities in traumatic injuries of the head from the medico-legal angle.

When neurologic manifestations follow immediately a head injury, a demand for indemnity in case of insurance or other forms of responsibility is justifiable. In cases of a retarded or a much delayed symptomatology a question will always be raised by the responsible side of the litigation as to the relationship between the trauma and the clinical picture. P. Béhague in his work entitled "*Questions neurologiques d'actualité*, 1922" based on a large experience during the World War concludes together with P. Marie that the period of latency between the trauma and the onset of neurologic manifestations is never above 18 months. Although in the present series of carefully collected cases the longest latent period was eleven months, nevertheless the writer recalls several cases in which morbid symptoms made their gross appearances at a much later date than 18 months. The above mentioned "small signs" had been either overlooked or the patients could not be seen and carefully examined. The group of cases here described, the knowledge of the existence of transient, fleeting but frequently repeated neurologic manifestations during the period of latency and the strict chronological tracing of them until they become grossly evident, finally and especially, the pathological data supplied

above showing the gradual development of degenerative changes of the brain tissue—are all evidences to prove the thesis of a direct relationship between a traumatic injury of the head and much delayed pathological phenomena. All these facts must be taken into consideration when one is confronted with the problem of the degree of invalidism in cases of traumata with late manifestations of organic nervous disorders. Personal experience shows that many traumatic cases occur in neurologic practice with late and very late manifestations when no indemnity is claimed, but very few cases come under observation when the question of compensation for infirmities caused by former accidents comes up for legal contention. The reason of the latter lies either in the omission on the part of the patient and the physician to even consider in the remotest way any relationship of the symptoms to a long past accident, especially if the latter was apparently slight or when a small

scar is present externally at the level of the old injury, or else when the usual signs of concussion were either absent or very slight. Quite frequently traumata are forgotten. Insurance companies or compensation boards usually give recognition only to cases in which the morbid manifestations appear shortly after traumata. The anatomoclinical considerations, as well as the physiological and experimental facts presented in this work favor a more just and fair relationship towards the incapacitated individual whose infirmity may be due to an injury inflicted by responsible agencies even if it occurred a long time prior to the appearance of gross morbid manifestations in the domain of the central nervous system. This contention is based on scientific data well proven to be of unquestionable value. Scientific facts serve the ends of justice in a more adequate manner than any other consideration.

# Carnosine as a Possible Factor in Shock\*

By EDWARD C MASON, M D, Ph D, AND SAM BINKLEY, B S, A B,  
*Oklahoma City, Oklahoma*

THE investigations of Gulewitsch and Amiradzibi<sup>1</sup> led to the discovery of carnosine in beef muscle extract Von Furth and Schwarz<sup>2</sup> found that carnosine accounted for 30 to 44 per cent of the total extractive nitrogen of the skeletal muscle of the horse and dog Applying similar methods, Guglia and Constantino<sup>3</sup>, also Von Winiwaite<sup>4</sup> concluded that about one-third of the extractive nitrogen contained in skeletal muscle was in the form of carnosine

Carnosine has the following properties<sup>5</sup> "100 grams water at 24.9-25 degrees dissolve 3.1 grams carnosine It is precipitated from water by alcohol The nitrate melts at 222 degrees Colorless needle shaped crystals, m p 219 degrees with decomposition Carnosine tastes insipid and reacts strongly alkaline It is not precipitated by  $K_4FeC_6N_6$ , lead acetate, acid or basic, nor by  $HgKI_2$  Saturated picric acid does not precipitate it, but tannic and phosphotungstic acids do" On hydrolysis it yields histidine

From a review of the literature we came to the conclusion that little has been done to establish the biological significance distribution and fate of carnosine in the body Also, previous

studies involving the use of fresh tissue extract, autolyzed tissue extract<sup>6,7,8</sup> and the toxic condition accompanying burns<sup>9</sup> have suggested to us the possibility of carnosine being the toxic agent We have undertaken the following study in an attempt to add to our knowledge of this subject

## PROCEDURE

We were unable to obtain carnosine on the market but were fortunate in obtaining a gram of carnosine nitrate from George Hunter of the Department of Biochemistry, University of Alberta<sup>10</sup> Due to the limited amount of the preparation, we were unable to develop our studies as completely as we would have liked

Figure I is a tracing obtained from a dog weighing 9.8 kilos, the tracing is a record of respiration and blood pressure It will be noted that the injection of 1 c c or 1 grain of carnosine nitrate caused a definite change in the respiration and also a fall in blood pressure The second injection containing two grains of carnosine nitrate gave similar but more pronounced results

In order to test the part played by the vagal endings we next gave the dog 1 mg of atropine sulphate Figure II is presented to show the effect of atropine administration during vagal stimulation The atropine was administered

\*From the Department of Physiology, University of Oklahoma School of Medicine



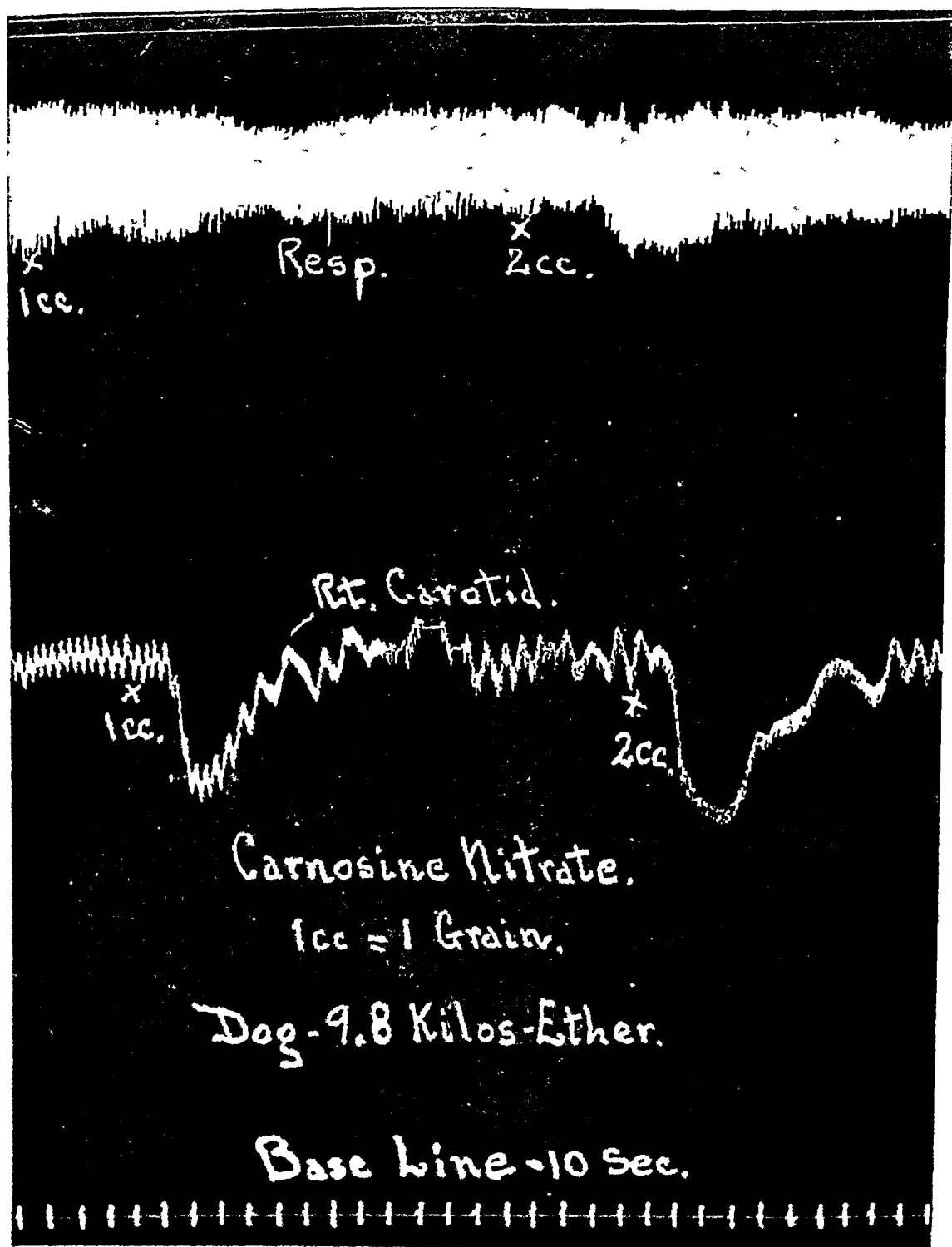


FIG. 1

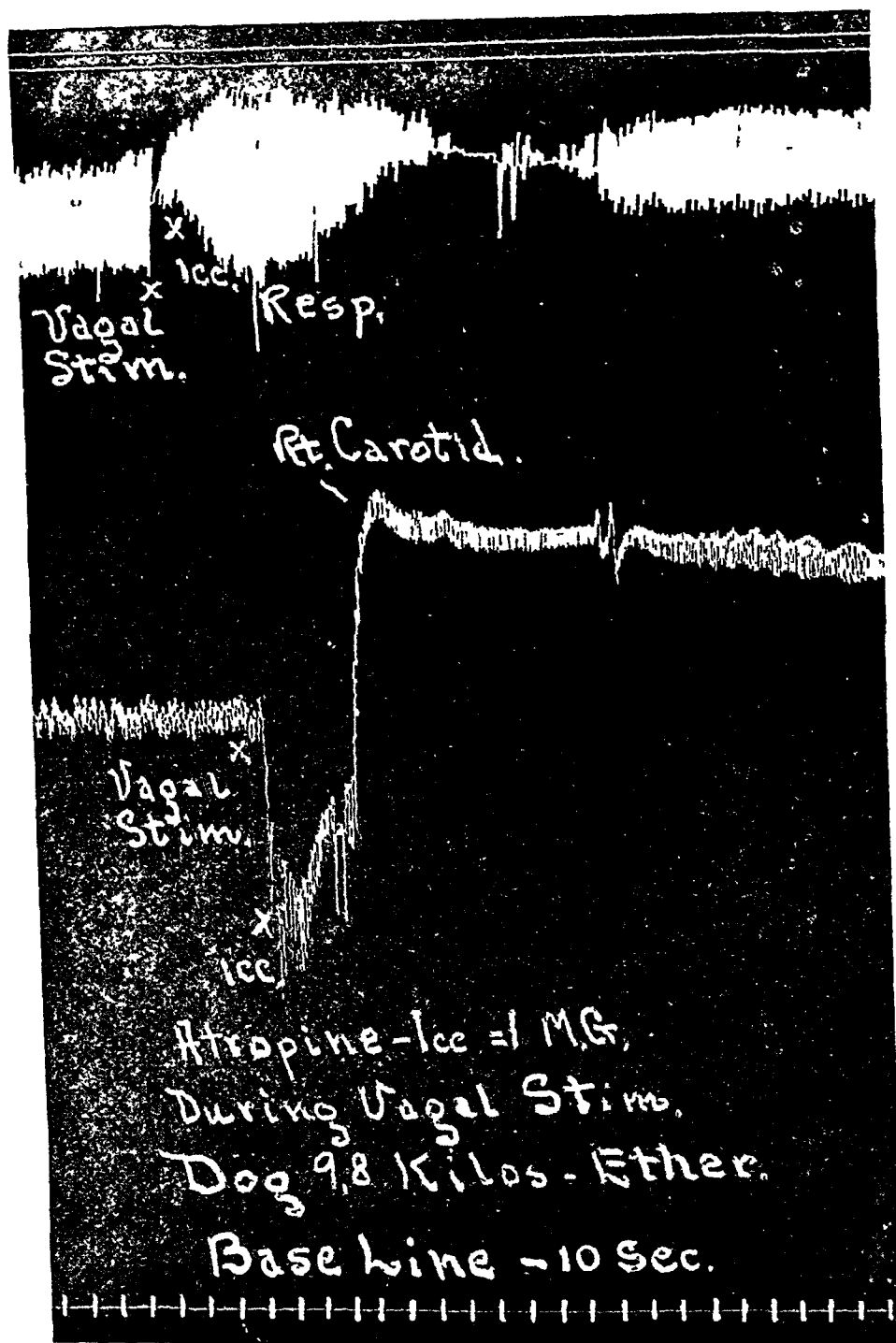


FIG II

while the blood pressure was low and the heart rate very slow. With the action of atropine the heart became rapid and the blood pressure rose above the previous normal.

Figure III was obtained following the action of atropine and represents the action of 15 grains of carnosine nitrate. It will be observed that the fall in blood pressure was greater than that produced by previous doses of carnosine. It is evident that the action of atropine on the para-sympathetic system does not inhibit the action of carnosine.

Figure IV is a record obtained from a dog weighing 19 kilos. It is a myocardiograph obtained by the Jackson apparatus. The chest was open and therefore the animal required artificial respiration. The drum was moving rapidly enough to show the nature and amplitude of the individual heart beats. The animal received only one injection of carnosine nitrate, the dose being 2 grains. It will be noted that the action of the compound was rapid, there being a sudden fall in blood pressure with the slowing of the heart and a decrease in amplitude. In this particular case carnosine nitrate proved to be quite toxic.

In attempting to find the point of action of carnosine we extended our studies to include the central nervous system. Figure V represents the blood pressure obtained from a dog weighing 12.2 kilos, pithed brain and cord. The injection of two grains of carnosine nitrate caused a definite fall in blood pressure and the repeated injection of the same size dose gave a similar response. It is evident that carnosine exerts some action after the destruction

of the central nervous system. However, the response is not so great as in the intact animal.

Figure VI is a record of respiration, spleen volume and blood pressure, obtained from a dog weighing 12 kilos. In this particular animal 1 grain of carnosine nitrate had but little effect, however, it will be noted that spleen volume fell with the fall in blood pressure. This suggests that the fall in blood pressure accompanying the injection of carnosine nitrate is not due to increase in the volume of the viscera.

### DISCUSSION

Mason et al have carried on several studies<sup>6,7,8</sup> in an attempt to determine the toxic substance liberated during the autolysis of tissues. While carrying on these studies the idea was conceived that the toxicity accompanying burns was due, in a large measure, to the absorption of the products of autolysis. Since such burns were usually sterile it was decided that the toxic fraction came from the patient's own dead and dying tissues and not from any bacterial action. Davidson<sup>9</sup>, at the suggestion of Mason, instituted the use of tannic acid as a treatment for burns. The splendid results obtained by Davidson, which have been so abundantly confirmed by others, strongly suggest that tannic acid precipitates the toxic fraction and holds it in an insoluble precipitate.

From the properties of carnosine, listed in the early part of this paper, it will be observed that carnosine is precipitated by tannic acid. It is therefore suggested that carnosine may be a toxic factor contributing to the mortality accompanying burns.

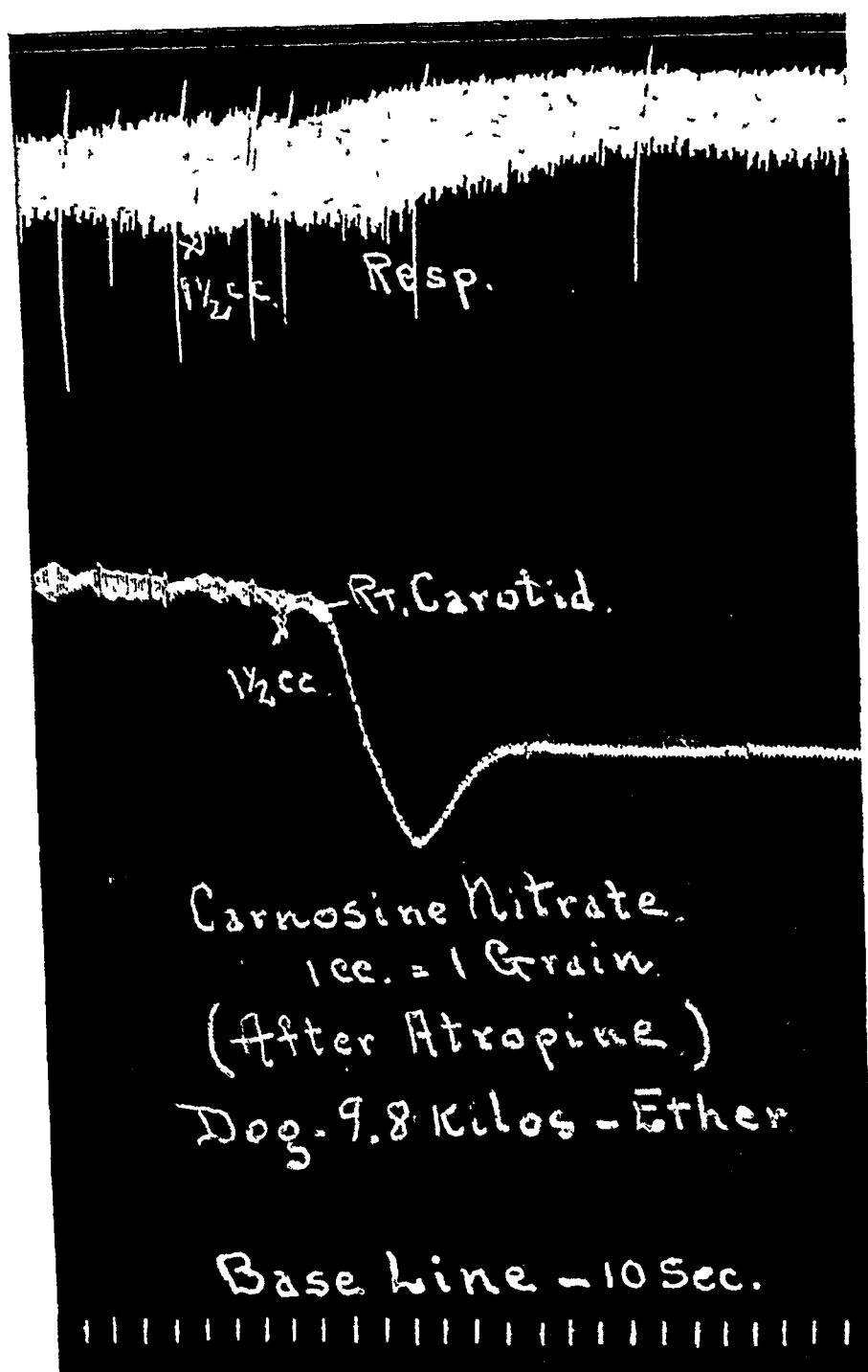


FIG III

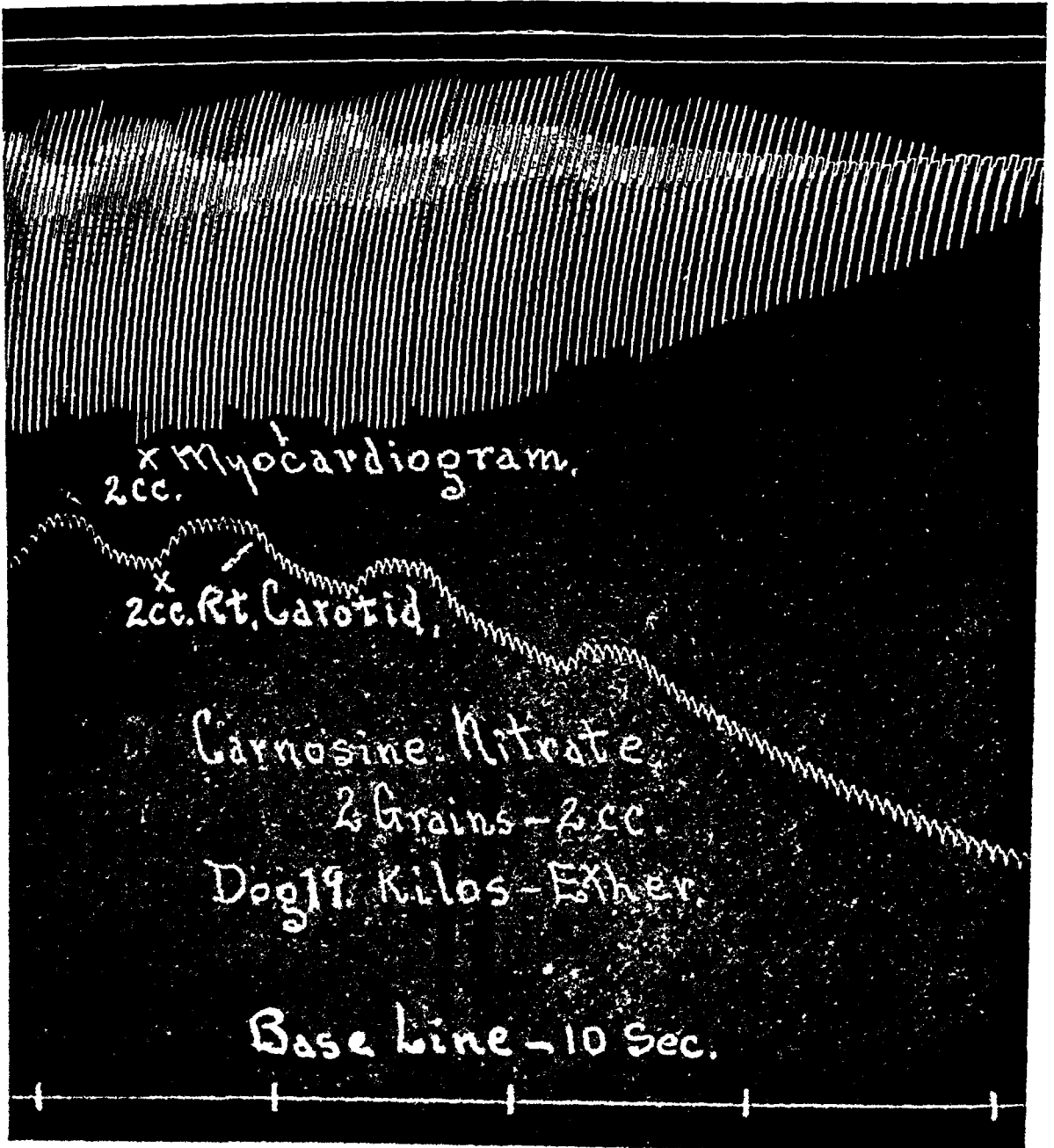


FIG. IV

In a recent paper<sup>11</sup> we have attempted to determine the toxic substance generated during autolysis of body tissues. Such autolyzed tissue extract was treated with an equal volume of 4% tannic acid and filtered. The clear filtrate proved active and from such results it is suggested that carnosine is not the principal toxic substance in autolyzed liver tissue.

Our records have confirmed many of the points observed by Schwarz and Goldschmidt<sup>12</sup> and we have observed

that carnosine in many ways acts similarly to histamine.

### CONCLUSIONS

1 Carnosine occurs in considerable amounts and is sufficiently toxic to be a probable factor in contributing to shock.

2 Carnosine acts after the destruction of the central nervous system and after the destruction of the parasympathetic endings.

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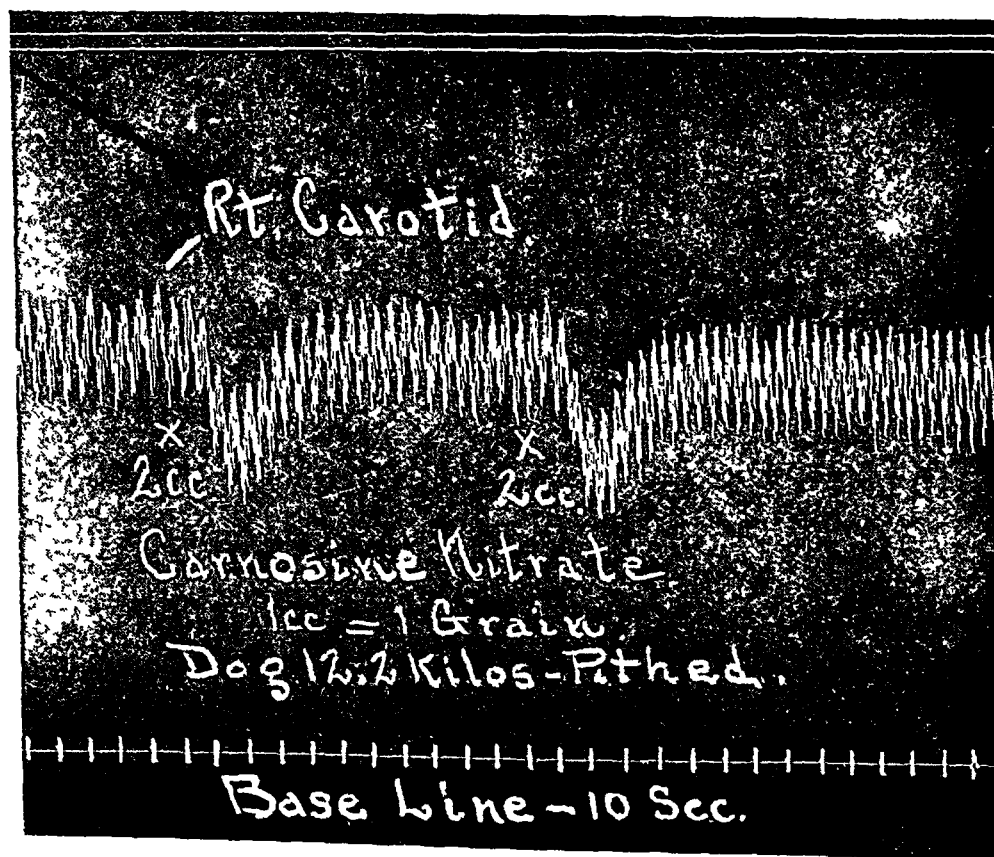


FIG V

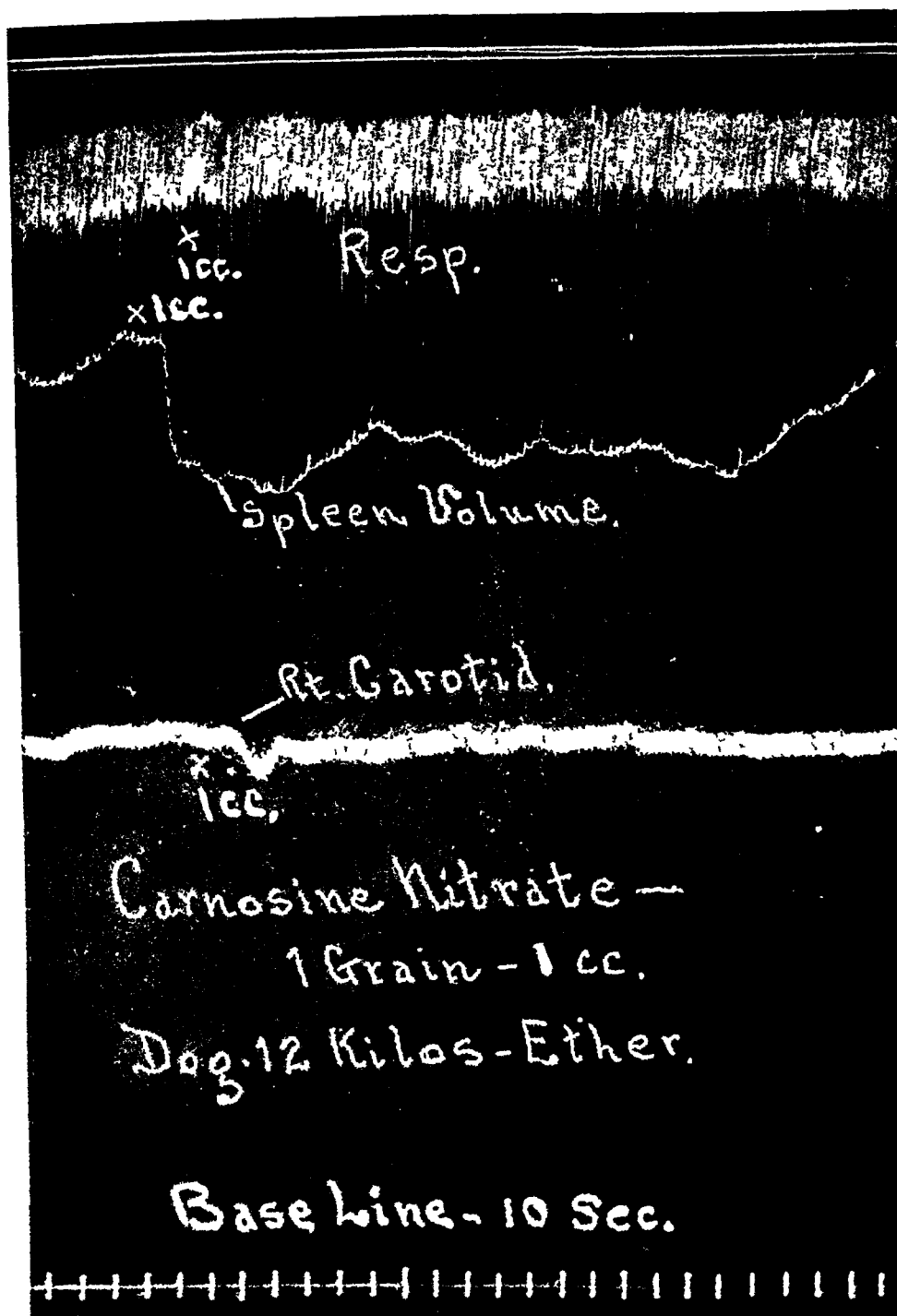


FIG. VI

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# Preventive Treatment of Bronchial Asthma and Hay Fever\*

BY LEON UNGER, S. B., M. D.

*Assistant Professor Department of Medicine, Director Asthma and Hay Fever Clinic, Northwestern University Medical School, Chicago*

THE prophylactic treatment of bronchial asthma, hay fever and other allergic diseases has been much neglected. While other phases of these diseases have received increasing attention very little attention has been given to ways and means of preventing these illnesses.

"Allergy" is hypersensitiveness or idiosyncrasy occurring in man. Many different parts of the body may be affected and symptoms will naturally depend on the part involved, and thus we may have the different members of the allergic group, namely bronchial asthma, hay fever or pollenosis, hyperesthetic or allergic or vasomotor rhinitis, gastro-intestinal or abdominal allergy, —sometimes called food allergy, eczema, especially in children, urticaria and angio-neurotic edema, and allergic bronchitis. Migraine, epilepsy, certain purpuras, certain joint and bladder disturbances may also belong to this group, but their place is more debatable.

## ETIOLOGY

The cause of this entire group of diseases is based on three main factors:

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\*From the Asthma and Hay Fever Clinic Northwestern University Medical School, Chicago.

Heredity is probably the underlying cause. Practically all investigators agree that in 60% of cases there is a history of one or more cases in other members of the family. Furthermore, it has been shown that where both parents are allergic the offspring have about twice as much chance of suffering themselves as where only one parent is affected. And, where neither parent is a victim the children are not at all likely to develop one or more of these sicknesses. It has also been demonstrated that the greater the hereditary influence the earlier do the symptoms of allergy occur in the offspring although the children need not inherit the same disease, e.g. the parent may have hay fever and the child asthma.

The second factor in the etiology of allergy is the exciting cause or causes. These may be placed in several groups, such as pollens, animal hairs and danders, foods, dust, and odds and ends like orris root, aspirin or quinine. Most patients are sensitive to more than one of these exciting causes. These materials constitute the trigger which when associated with the inherited basis sets up the condition we know as bronchial asthma or hay fever or one

or more of the other members of the group

The third factor is made up of the contributory influences, such as dampness, change of weather, fumes of all kinds, nervous phenomena, over-eating, and broncho-pulmonary infections. They alone do not cause asthma or hay fever, but, nevertheless, they must not be neglected

#### BRONCHIAL ASTHMA AND COMPLICATIONS

Bronchial asthma is the most serious of the allergic diseases. It usually starts in childhood or young adult life and gives the characteristic history of attacks of wheezing, dyspnea and cough. At the onset these children are usually free from symptoms between attacks, but, as one spell follows another the two main complications set in, namely, emphysema and chronic bronchitis. These two tend to change the picture. The periods of complete freedom between attacks vanish, and, instead, we find that the patients are short of breath on a little exertion and cough more than formerly. Unfortunately, with the onset of the emphysema and chronic bronchitis, the prospect for complete relief of symptoms becomes less bright.

#### PREVENTIVE TREATMENT

The preventive treatment of allergy may be divided into two main headings, the prevention of attacks and the general prophylactic measures.

There are many methods we use to prevent attacks, especially of hay fever and bronchial asthma. We may divide them into three main groups, elimination, desensitization, and symptomatic measures.

Elimination is the most important of these and should be done as thoroughly and as completely as possible. Foods which cause trouble can be completely removed from the diet, but we must remember that eggs, wheat and milk are contained in many foods not ordinarily thought of. For example, it is not sufficient to ask an egg-sensitive individual to keep away from eggs, he must also avoid all foods which contain eggs.

It is not so easy to remove air-borne materials, such as dust and pollens. Dust can be lessened by using simple furniture, by frequent vacuum cleaning, and by covering mattresses and pillows. In severe cases air filters have given excellent results both here and in Europe. Pollens like ragweeds can be avoided by going where these do not grow, e. g. Europe or California. Animal danders and feathers can usually be completely eliminated and often with most gratifying results. For example, removal of a dog or substitution of a kapok pillow for a feather one will often be quite effective. Patients who are sensitive to orris root which is contained in many face powders and talcum must be made to stop these altogether or to use brands which are free from orris root.

Desensitization is to be tried when the exciting substances cannot be entirely avoided or when they cannot be avoided over long periods of time. We therefore try to desensitize those patients who are hypersensitive to most of the air-borne materials, such as animal derivatives, pollens, orris root and house dust, and to the three main foods, eggs, wheat, and milk.

Symptomatic or non-specific treatment consists especially of the use of a large number of drugs especially epinephrin and ephedrin and removal of foci of infection, e g infected sinuses. Change of climate, in our experience, has helped very few.

It is highly important, also, that the contributory factors should be avoided as far as possible,—such as wet feet, over-exertion, over-eating, excitement, etc. Attention to these helps.

All this brings us up to the question of how to prevent the onset of bronchial asthma, hay fever and the others. What can we do to keep these diseases from starting?

The solution to the problem reveals itself when we recall that the two main factors in the etiology are hereditary background and the exciting causes. Each of these can be successfully attacked.

As shown previously, heredity is so important in allergy that the majority of cases are affected by it. The obvious conclusion and remedy is to discourage marriage between victims of any of these sicknesses. Let us advise our hay fever patient not to marry another hay fever case or an asthmatic or one who has urticaria or hyperesthetic rhinitis. Such marriages will be very apt to bring forth children who will be similarly afflicted. Propaganda like this will ultimately reduce the number of allergic cases and is certainly a step in the right direction.

The exciting factors can also be successfully attacked. Several measures stand out as most important.

First of all, all children of parents who have hay fever or asthma should be considered as potential allergics

even if they are free from symptoms. Since the chief exciting causes are foods and inhalants prevention can be carried out easily. Foods, for example, should be closely watched from the time of birth. Foods to which the child is sensitive will show themselves by causing gastro-intestinal upsets, by frequent attacks of rhinitis or bronchitis or eczema or urticaria. When the offending food is removed the symptoms will usually disappear more or less promptly. It is very important to add one new food at a time and to wait several days, at least, before judging as to its value to the child. By being careful the parent or the physician can usually detect quite early which foods, if any, are causing symptoms and these can be removed from the diet before any serious trouble such as asthma has occurred.

Air-borne substances can be avoided, at least to a great extent. Animals should be forbidden in any home where allergy exists. This applies especially to dogs, cats and horses which are common causes of trouble. Hair mattresses and feather pillows should either not be used or should be well covered by oiled silk or light rubber sheeting. Certain toys are covered with rabbit hair or furs and may cause trouble. Fur coats or coats with pieces of fur should also be avoided. It is well to remember that substances which are inhaled usually cause frequent attacks of rhinitis and bronchitis before asthma occurs,—these are the warning signs. Children of allergic parents should either not use face or talcum powders at all or should use a brand which is free from orris root.

Certain drugs should also be used cautiously. Aspirin and quinine have frequently caused severe asthma and it is well to be careful with these in allergic families.

General hygienic measures, good food, care of teeth, removal of infected tonsils and adenoids—all these help in a general way and should receive proper attention.

These precautions carried out intelligently will ward off most cases of allergy or at least, will lessen the severity of the attacks should these occur.

Let us now consider cases where symptoms have already developed and see what can be done in a prophylactic way, especially as regards asthma. These patients may have hyperesthetic rhinitis, or frequent bronchitis (so-called allergic bronchitis), or eczema or urticaria or hay fever. Any one of these may be and frequently is followed by bronchial asthma, if neglected, or if treated improperly. These cases are very numerous and exceedingly important and we must emphasize again that these diseases are all in the same group and complicate one another. For example, eczema in infancy is a very common forerunner of asthma in older life.

These patients should be examined and thoroughly skin-tested as early as possible and put under the proper treatment. For example, we know that about 40% of hay fever patients develop bronchial asthma sooner or later. Yet, many parents and physicians allow these sufferers to go on year after year without attention. They do not realize that the therapy of hay fever has advanced greatly in the last few years. It has been known for many

years that the symptoms of hay fever are due to certain pollens which are spread by the wind at certain times of the year, and we have been treating cases by injecting pollen extracts of the important weeds. Our results have been fairly good, averaging about 25% complete relief and an additional 60% improvement. Recently, it has been demonstrated without question that about two thirds of all hay fever cases are also sensitive to other substances besides the pollens which cause their hay fever. These other substances are very important and although they may not cause the patient much trouble by themselves they aggravate the effect of the pollen and make the condition worse than it would otherwise be. And it is most gratifying to be able to say that removal of these other substances, especially during the hay fever season, substances like orris root or egg or wheat, has helped our results tremendously.

This represents a great advance in hay fever work and in the prevention of asthma, and for the past year or two we have been making complete protein as well as pollen tests on all hay fever cases. Another step forward has been the adoption by many of us of all year round or perennial treatment of hay fever.

The other conditions which frequently precede asthma should likewise receive prompt attention. Eczema should not be neglected or treated merely as a skin disease. The eruption may be a manifestation of hypersensitiveness and good results will follow thorough skin testing and elimination of the offending food or foods.

Patients with hyperesthetic or allergic rhinitis are very numerous and all too frequently they go from one nose and throat specialist to another without relief, and many develop asthma.

Bronchitis in children is very common and some of these may be classed as allergic. These occur in children who have spasmodic cough without dyspnea. Ephedrin and epinephrin usually clear them up and very often there is a family history of allergy and other findings of hypersensitiveness, such as eczema and urticaria. If neglected these attacks of bronchitis often increase in severity until dyspnea occurs and we now call the condition bronchial asthma.

In summarizing preventive measures the first essential is to make the diagnosis of allergy early and this is not difficult if the possibility is thought of. In taking histories let us inquire whether there is allergy in the family, just as we ask about tuberculosis. And the finding of parents with asthma or hay fever or the history that the child has had eczema or other manifestation should make us suspect some allergic condition and treat accordingly. Our second essential is to skin test thoroughly and completely and to treat intelligently. Above all, let us try to prevent the onset of these sicknesses.

## CONCLUSIONS

1 The chief allergic diseases are bronchial asthma, hay fever, hyperesthetic rhinitis, alimentary allergy, allergic bronchitis, eczema and urticaria.

2 The etiology is dependent upon a hereditary basis, certain well-known exciting causes, and numerous contributory influences.

3 Skin tests should be made as early as possible, should be carried out completely, and backed by clinical trial.

4 Attacks of these diseases can usually be prevented by the proper treatment, which consists of elimination, desensitization in certain cases, and symptomatic measures where indicated.

5 The very onset of allergic diseases can often be avoided by

- (a) Advising against intermarriage between allergic individuals
- (b) Guarding children of allergic parents against foods to which they may be sensitive and against air-borne substances

6 The onset of the milder members of the group, e. g. eczema or hay fever, calls for prompt measures to ward off the later development of bronchial asthma.

# An Agranulocytic Blood Picture with a Pneumococcic Septicemia

BY SHERBURNE CAMPBELL, M D, AND THOMAS P MURDOCK, M D.  
F A C P, Meriden, Conn

**A** VOLUMINOUS literature has developed on the subject of agranulocytic angina since Schultz<sup>1</sup> first described the condition in 1922. Most of the cases reported to date have been the so-called pure cases in which the blood picture was that of an agranulocytosis, without complication, and without an associated incidental condition.

Turk<sup>2</sup> has reported a case in which there seemed to be a very definite connection between the sepsis of the lip and mouth, and the blood picture. The organism from the pus was staphylococcus aureus.

Blumer<sup>3</sup> reports the observation of four cases and reported one. In this case there was present a large abscess of the left thigh. Culture showed staphylococcus aureus.

Allen<sup>4</sup> reported a case of agranulocytic angina with thrombopenic purpura.

The general impression is that most cases, whether of the pure variety or not, die. However, Kastlin<sup>5</sup> has reviewed forty-three cases in which three cases recovered. Hutcheson<sup>6</sup> has reported five cases with two recoveries. Hulper<sup>7</sup> in a review of the literature in 1928 reported six recoveries. Recently Roberts<sup>8</sup> and his associates were

permitted to follow a case of agranulocytic angina through a period of several remissions and relapses.

*Case Report*—Mrs A W Age 60 yrs Widow. On July 17th, 1930 the patient complained of a sore throat, accompanied by a slight elevation of temperature. On July 20th her condition became worse. She was prostrated, throat symptoms more marked, temperature high. On July 22nd, the case was referred to the hospital by Dr E M Simmons of Southington, Conn. The past history showed the patient to have had measles at thirty years of age, and scarlet fever at forty-five years of age. The latter was complicated by "rheumatism" which lasted about one year. She has had repeated attacks of tonsillitis. The family history showed one sister living and well. Mother died of an accident, and the father died of Bright's disease.

*Physical Examination* On admission to the Meriden Hospital patient was somewhat irrational, cyanotic and restless. Temperature 103°, pulse 130, respirations 30. The right tonsil had a medium sized patch of grayish exudate. The posterior cervical glands on both sides were enlarged and tender, more so on the right. The submaxillary gland on the right was also involved. There was no rigidity of the neck. The heart was rapid and regular. There were no murmurs, and it was not enlarged. The blood pressure was 160/80. The right lung was dull at the base, and râles were heard in both bases. The abdomen was distended and tympanitic. The liver and spleen could not be palpated.

*Laboratory Findings* The blood picture on the morning of the 23rd was as follows Erythrocytes 3,680,000, Leucocytes 200, Hemoglobin 80%, Polymorphonuclears 8%, Small Mononuclears 64%, Large Mononuclears 28% Urine 1014, acid, cloudy, albumin large amount, and many granular casts The throat smear showed a few fusiform bacilli, and some spirillae The throat culture was negative for diphtheria, but did show many mixed cocci including staphylococcus aureus, and streptococci

*July 23rd/30* The patient continued to grow worse She became very irrational Cyanosis was more marked Breathing was labored Temperature went up to 105°, the pulse to 140, and the respirations to 48 On this date she was given 500 cc of unmodified blood intravenously The advisability of x-ray therapy was discussed but it was our opinion that she was too ill to be transported to the x-ray department

*July 24th/30* The blood picture on this date and after transfusion was Erythrocytes 3,840,000, Leucocytes 100, Hemoglobin 80%, Polymorphonuclears 15%, Small Mononuclears 65%, Large Mononuclears 15% The blood culture was positive for pneumococci The patient died at 6 30 p m

*Positive Autopsy Findings Tonsils* The right tonsil is definitely necrotic and ulcerated Microscopically there are areas of necrosis in the lymphoid tissue At one area there is destruction of the surface epithelium of the tonsil and great numbers of bacteria are present and infiltrating the adjacent tissues There is no evidence of inflammatory reaction Deeper down in the tonsil are spaces which are presumably crypts but the superficial cells have been destroyed and there are masses of bacteria here These bacteria prove to be large gram positive bacilli, some of them quite granular, some straight but many of them a little curved Other bacteria are gram positive cocci, occurring chiefly in pairs or small groups, but not in chains

*Heart* The heart shows two pink warty excrescences on the mitral valve and shortening and thickening of one of the leaflets of the valve The musculature of the left ventricle shows definite scarring, particularly

in the region of the apex where there is a grayish scar  $3/4"$  x  $1/3"$

Microscopically the muscle fibers are large as is seen in hypertrophy and there is considerable replacement of the muscle fiber by fibrous tissue Sections of the heart valve show the granulation there to be fibrous, and not the result of an acute process

*Lungs* The left lung shows a deep black mottling all over, more marked in the lower lobe The right lung presents a picture similar to the left with the addition of dense adhesions over its surface Microscopically there is chronic vesicular emphysema, together with thickening of the pleura, and irregular fibrous thickening of the walls of the air-spaces Another section of the lung shows air-spaces filled with blood, and in other areas there is a white fibrous tissue and masses of bacteria which prove to be cocci There is no inflammatory reaction around these bacteria

*Liver* The liver is very pale There is considerable yellowish discoloration around the central vein Microscopically it shows acute parenchymatous degeneration

*Kidneys* The left kidney is slightly swollen On section the capsule is everted, leaving a slightly granular surface The markings are very poor The cortex is variable in thickness and there is diffuse yellow mottling throughout Microscopically there is diffuse chronic nephritis, with arteriosclerosis and marked parenchymatous degeneration

*Tibia* The bone marrow is yellow and serous in consistency Microscopically it shows practically no cells There is some fat present, but this appears to be less than normal

## CONCLUSION

A search of the literature has revealed few cases of pneumococcic septicemia with an agranulocytic blood picture Babbitt and Fitz-Hugh<sup>6</sup> have reported that positive blood cultures including pneumococci were obtained in several cases On the contrary one expects to find a marked leucocytosis with pneumococcic septicemia Several writ-

ers have called attention to the fact that cases of lobar pneumonia with, or without pneumococci in the blood-stream, and with a leucopenia, show a very high mortality. It is uncertain whether the blood-stream infection is primary or secondary as related to an agranulocytic picture. Perhaps, however, in this patient the necrotizing condition in the throat would point toward an agranulocytic angina, complicated by a pneumococcic septicemia.

It is a pity that it is not possible to study more cases of agranulocytic an-

gina prior to the onset of complicating or incidental conditions. The violent illness of this patient, disproportionate to the extent of her throat pathology, makes us consider the theory that agranulocytic angina is a separate entity, and that if one were permitted to follow the usual case from the beginning, one would see several relapses and remissions during its course. Probably due to the absence or reduction of the number of granulocytes, the patient is less able to combat acute infections.

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# Relative Blood Volume Changes Following the Use of Intravenous Glucose Injections in Pneumonia\*

By JOHN H. L. HEINTZELMAN, M. D., *Pittsburgh*

**A**T THE present time, as glucose solutions are used intravenously in certain diseases, particularly in pneumonia, the effect produced on the vascular mechanism is of paramount interest.

A review of the literature on the subject of blood volume changes following intravenous injections of hypertonic glucose solutions shows that the majority of investigators demonstrated an increase in the volume<sup>1, 2, 4, 5, 6</sup>. Two writers state that there is no change in the blood volume following glucose injections<sup>7, 8</sup>. Such investigations have been chiefly on animals. The conclusions were based on comparatively few observations, and these were not uniform.

Twenty-six relative blood volume determinations were made. Twenty observations were obtained from patients ill with pneumonia, and six from a patient having multiple neuritis.

The method of determining the relative blood volume changes was as follows: 0.5 cc. of oxalated blood was diluted with water up to the mark in a 50 cc. graduated flask. The blood drawn before the injection of the glu-

cose was used as the hemoglobin standard of 100%. The samples drawn after injection were compared with this standard in a colorimeter. The standard was set at 10. When a reading had been made on the unknown sample, the blood volume was determined as follows:

The reading of the unknown divided by the reading of the standard, multiplied by one hundred, equals volume per cent.

Emphasis is placed on the fact that in the twenty-six observations, every one showed an increase in the relative blood volume following an intravenous injection of 200 cc. of 25 per cent glucose solution. Table I. The average increase in blood volume was 19.5 per cent. Ten oxygen capacity estimations, Table II, and eight hematocrit tests, Table III, indicated relative blood volume changes in agreement with colorimeter findings.

Blood samples were taken immediately and at approximately twenty and forty minutes after the end of the injection periods, and seven observations were made by all three methods to determine how long the increase in relative blood volume was sustained. The results showed that

\*From the Department of Physiology, School of Medicine, University of Pittsburgh.

TABLE No I  
BLOOD VOLUME

Case	Before Injection	Increase Immediately After Injection %	Increase 20 Min After Injection %	Increase 40 Min After Injection %
I	Taken	8.7		
II	as	16.4		
III	Standard	14.2		
IV		25.4		
V	100%	56.2		
VI		1.2		
VII		43.4		
VIII		17.4		
IX		9.0		
X		23.9		
XI		25.6		
XII		26.4		
XIII		17.0		
XIV		28.7		
XV		4.7		
XVI		22.7		
XVII		15.8		
XVIII		26.8		
XIX		19.4		
XX		6.4		0.0
XXI		31.3	1.5	0.0
XXII		11.3	5.1	0.3
XXIII		10.8	5.8	2.3
XXIV		16.8	6.7	0.0
XXV		13.8		4.8
XXVI		13.4	1.0	0.6
Average Increase		19.49	4.0	1.2
Volume %	100	119.5	104.0	101.2

Blood Volume changes following injection of glucose solutions as determined by colorimetric estimations of hemoglobin

Cases 20 through 26 show the volume returning to near normal within about one hour

TABLE No II  
OXYGEN CAPACITY

	Before Injection	Immediately After Injection	20 Min After Injection	40 Min After Injection
XVI	21.83	21.07		
XVII	18.77	15.79		
XVIII	20.10	16.38		
XIX	18.77	15.71		
XXI	18.96	12.47	17.56	18.39
XXII	15.69	14.30	14.46	15.21
XXIII	17.33	14.38	17.72	
XXIV	20.17	16.83	17.98	18.44
XXV	23.35	21.82		23.58
XXVI	22.91	22.10	23.46	
Average	19.76	17.08	18.24	18.9

Oxygen Capacity results in volume per cent confirming colorimetric findings

TABLE No III  
HEMATOCRIT

Case	Before Injection	Immediately After Injection	20 Min After Injection	40 Min After Injection
XVI	41 0	35 0		
XVII	40 0	35 0		
XVIII	36 0	27 0		
XIX	35 0	32 0		
XXI	29 0	24 5	33 0	
XXIII	31 0	26 0	28 0	33 0
XXIV	38 0	25 0	33 0	30 0
XXVI	41 0	38 0	42 0	38 0
Average—	36 3	30 3	34 0	33 6

Hematocrit results confirming colorimetric findings

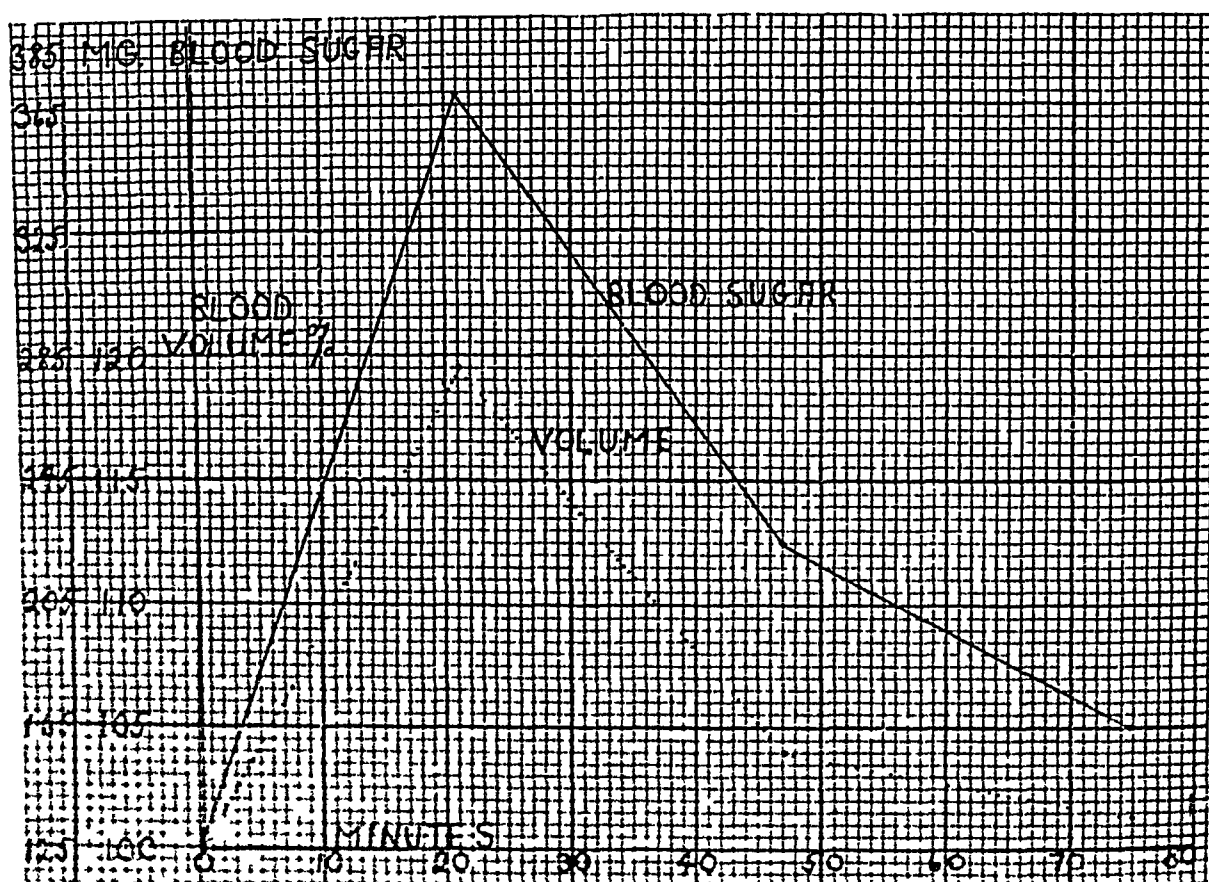


Chart I showing relation of Blood Volume to Blood Sugar following glucose injections

the volume returned to its former level within one hour

In addition to studying the volume changes, blood sugar determinations were made on the same blood samples to establish any relation that might ex-

ist between the hypervolemia and the hyperglycemia. All of the twenty-six observations showed a very marked increase in the blood sugar immediately after the injection of the glucose. This rise was followed by a fall with a tend-

ency to return to normal within one hour. The blood sugar did not return to normal, probably because the patients were receiving 200 cc of 25 per cent glucose solution intravenously every four hours independently of the injections used for the observations. The results plotted on graph paper showed that the increase in blood volume closely accompanied the increase in blood sugar. Chart I. This same finding has been recorded by others in dog experiments<sup>9, 10</sup>

#### SUMMARY

1. An intravenous injection of 200 cc of 25 per cent glucose solution into

patients having pneumonia, over periods of fourteen to thirty minutes, produced an immediate increase in the relative blood volume. The volume returned to, or nearly to, normal within one hour after the end of the injection.

2. The average relative blood volume immediately after injection in twenty-six observations was 119.5 per cent, an increase of 19.5 per cent.

3. Accompanying this hypervolemia there was a corresponding hyperglycemia. As the blood sugar curve tended to reach a maximum and then to return to normal it was closely accompanied by the blood volume curve.

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# Early Beriberi

By WILLARD S SARGENT, Lt (MC) U S N, *United States Naval Hospital  
Agaña, Guam*

**B**ERIBERI is a food deficiency disease. It is due to lack of vitamine water-soluble "B" in the diet. It is particularly prevalent in the Orient, Dutch East Indies and Brazil. It occurs mainly in those whose diet is principally or wholly rice, and especially milled rice.

In milling, the vitamine-containing portion of the rice is removed. The pericarp and aleurone layer are removed. Beriberi takes some time to develop, perhaps two to three months. It is not contagious. It seems that Wright's and Manson's and Braddon's theories are disproved. It is probably not due to bacteria, protozoa or nitrogen deficiency. There is possibly a toxin of metabolic origin formed. The absence of vitamins predisposes to infections in general. It is thought that excess carbohydrate intake with deficient vitamine "B" content is causative of beriberi and that it is not necessarily due to rice alone. When people are living on polished rice it seems that the largest eaters develop beriberi sooner, this suggests that the vitamine has something to do with carbohydrate utilization. The embryo has vitamins "A" and "B" both of which are lost in milling. The dust of the polshings has curative value. Undermilled or red rice is not so productive of beriberi.

The  $P_2O_5$  content of rice varies; that of polished rice is usually less than 4% while that of unpolished is 55% or more.

It would seem from the literature on beriberi that the dietary deficiency causes hypertrophy of the adrenals and that edema goes with this hypertrophy. The pituitary is not affected, while there are apt to be atrophic changes in the thyroid, testes, thymus and ovaries. Beriberi is found more frequently among the poor with bad hygienic and sanitary conditions. It is more frequent in men between 15-30 years of age.

I would, at this point, refer the reader to the experiments of Frazier, Stanton, Strong and Crowell and also the experiments of the Culion Leper Colony. (See Stitt's 'Tropical Medicine')

There are two types of beriberi. The wet form has affection of the vasomotor nerves and edema while the dry form has atrophic paraplegic manifestations in which muscle palsies or atrophies occur with Wallerian degeneration of the peripheral nerves. After all, the mixed form is more common than either one alone. A peculiar point about the multiple neuritis is the involvement of the tenth cranial nerve.

*Case 1* Japanese Age 23 Single Fisherman (Is working with case No 2 which follows) The diet for four months has been polished rice and fish, part of which was canned fish This is the first trouble like this he has ever had

For a week or so he has noticed his legs were swelling, the feet became puffy and his legs felt heavy and weak He tires easily He notes that the swelling pits on pressure and demonstrated same when asked his chief complaint He has no Romberg or Argyll-Robertson pupil No circumoral alteration of sensation is present His temperature is normal and the mind is clear He notices some dyspnea and palpitation on exertion He has no epigastric distress There is no sternal, scrotal or sacral edema He has a patch of edema on left arm about elbow region on extensor surface of forearm There is no tenderness over arms or hands but the calf muscles are sensitive Edema is present from middle of thighs down on both legs Sensation is impaired—pulling the hair is not nearly so productive of pain on legs as on arms

The patellar reflexes are sluggish and the arm reflexes are below normal in response

The B P is 100/76 The grip of the hand is weak A faint systolic murmur is heard at the apex but not elsewhere With the Jongkok test there is weakness shown but he could get up all right No altered sphincter action and no gastro-intestinal symptoms are present The heart palpitates on exertion The rate is 79 while reclining and 95 after a 50 minute walk The urine is normal, no albumin is present There is no fever and no effusion into the body cavities His Kahn is 4 plus and his blood count is just a little below average The stool is negative for hookworm

*Case 2* Japanese Age 19 Single Fisherman by trade For four months he has been working as a fisherman, hired to an employer, and his diet has been almost wholly polished rice and fish Apparently he was served some canned fish and most of the fish caught was sold by the employer

He has never before had any trouble like the present He first noted that he tired easily while doing his work or walking, his legs feel heavy, and he feels weak and not

able to do work as usual Working makes his heart pound and he has to breathe harder There is no epigastric pain or pathological symptoms The calf muscles are tender but the thenar and forearm areas seem normal There is no circumoral alteration of sensation The arm reflexes are normal but the patellar are sluggish There is edema over the tibia and sensation is not as well produced as elsewhere There is no edema of arms, sternal, or scrotal areas The B P is 105/80 The grip of the hands is weak The temperature is normal and the mind is clear There are no murmurs at the heart arch The foot is not "dropped" but is weak in muscle power The Jongkok test (while able to get up) showed difficulty in rising The sphincters act normally and there is no Romberg or Argyll-Robertson pupil The heart palpitates on exertion The rate is 85 at rest and 92 on walking There are no gastrointestinal symptoms

The urine is normal, no albumin is present There is no fever There are no effusions His Kahn test is negative and his blood count is nearly up to normal The stool is negative for hookworm

#### COMMENT

The urine in these cases is normal which tends to rule out nephritis Valvular heart disease and lung affections proved negative on physical examination The absence of the Argyll-Robertson pupil, Romberg and pain rules out tabes, and no ataxic gait was present These cases were not far enough advanced for the tripod gait The history, the absence of digestive symptoms, the lack of tremors, the normal mentality and the vagus involvement tend to rule out alcoholic neuritis The vasomotor phenomena, the absence of puffy eyelids and pigmented skin and lack of vagus involvement again rule out arsenical neuritis The absence of colic, basophila, blue line on the gums and the involvement

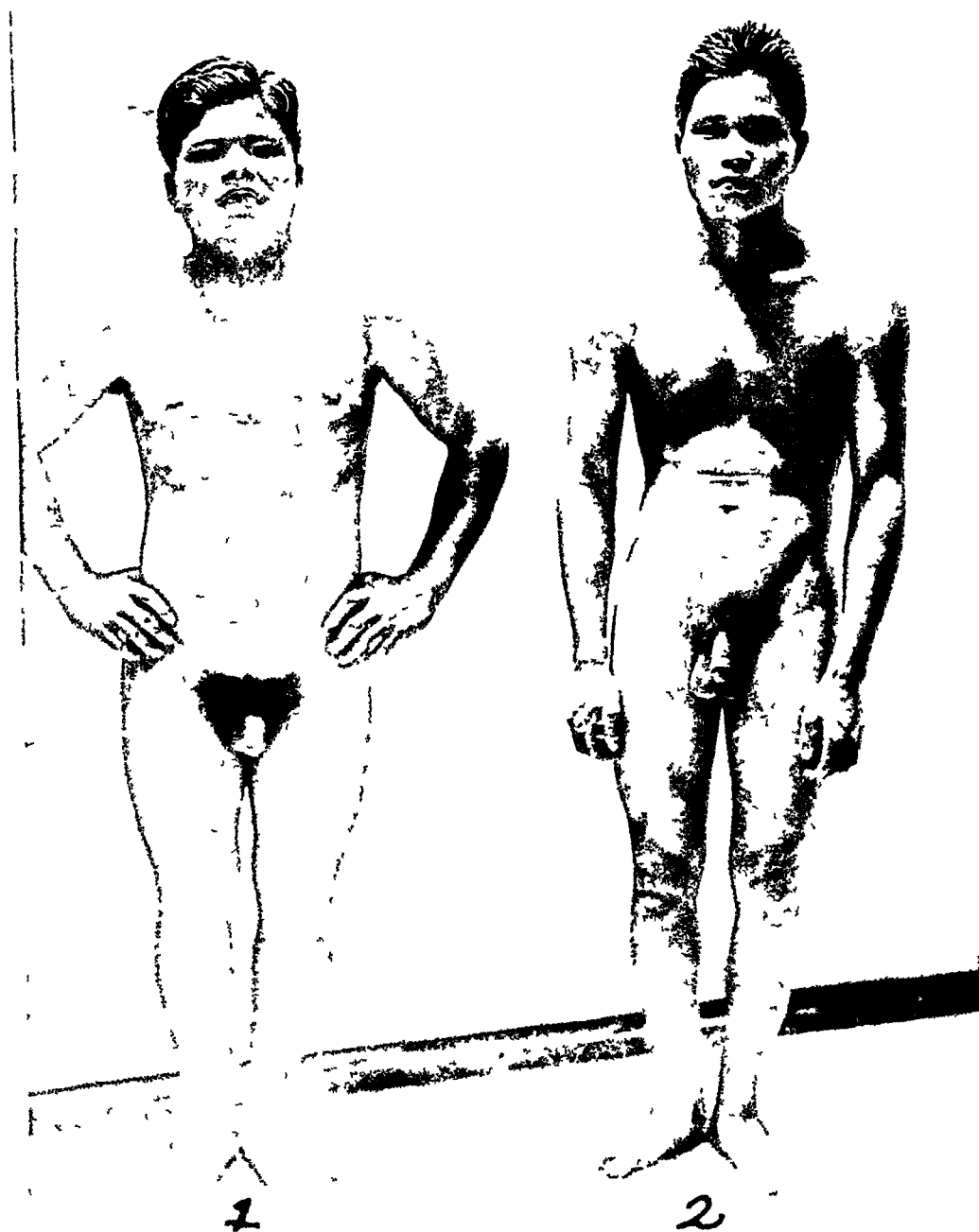


FIG. 1. Cases of early beri-beri. Both showed edema, but scrota are free from edema. Case No. 1 shows a patchy edematous area on left arm. Both patients became fatigued while the photograph was being taken.

of the lower extremities rather than the upper helps to rule out lead poisoning. The negative stool findings and the neurological findings speak against hookworm disease.

The history and age rule out infantile, prison, and asylum beriberi. The neuritis findings speak against ship beriberi. The lack of rash and fever rules out epidemic beriberi.

With the edema, the altered sensation, the poor reflexes, the signs of vagal involvement, the weakness and the history we feel that we can make a diagnosis of early beriberi here.

These cases were put to bed, kept in bed, and a diet prescribed. The diet given was meats, eggs, milk, liver, heart, vegetables and fresh fruit. Yeast was given several times daily. We could obtain no rice polishings here. Malt extract was not obtainable. The carbohydrates were slightly restricted. Atropin and strychnine were given regularly and massage was employed.

After two weeks, improvement began to be noticed and in about six

weeks the patients felt stronger, the edema disappeared, the heart slowed down and they were up and about.

The case with the positive Kahn was then given antiluetic treatment.

After discharge they reported back weekly for examination and check on diet. As prophylactic measures they were told what to eat and what to avoid. Butter was advised as it seems to prevent edema. Rice was scratched from the list. It has been said that parboiling the rice instead of milling it, while it causes a bad odor, causes the pericarp to adhere and helps keep the vitamins but this was not gone into in arranging the diet. The main things were fresh meat, fresh fruits and fresh vegetables. Barley, peas, beans and yellow meal were added. Potatoes were put in as a prophylactic. Onions were advised, but canned goods were tabooed.

Six months after discharge the cases were both well and showed no recurrence.



# Mitotic Leukoblasts In the Peripheral Blood of a Case of Acute Leukemia

By HAROLD BOWCOCK, M D AND ROGER W DICKSON, M D *Atlanta, Georgia*

**M**ITOTIC figures are always discoverable in the cells of the bone marrow, lymph glands, spleen and other tissues of patients dying of acute leukemia. The occurrence of mitotic leukoblasts in the peripheral blood of patients suffering from leukemia is either rare or the mitotic white cells have been falsely interpreted as mitotic erythroblasts. Dock<sup>1</sup> studied mitotic leukoblasts and erythroblasts and reviewed an extensive but uncertain literature. Tannhauser<sup>2</sup> described mitotic leukoblasts in the peripheral blood of a patient with acute leukemia. Bowcock and Bishop<sup>3</sup> reported a case of acute leukemia in which the peripheral blood frequently contained a type of mitotic cell, the characteristics of which showed a close resemblance to the mitotic cells which occur in the germinal centers of lymph glands. Another, and rarer type of division figure was more like a mitotic erythroblast. Bowcock has recently observed a third case of acute leukemia with many mitotic white cells in all stages of indirect division in the peripheral blood. Groat<sup>4</sup> has just recorded a beautifully illustrated case of myeloblastic leukemia in which he was able to picture all stages of mitosis from spireme to

telephase. At the same time, Rabino-vici<sup>5</sup> reported a case of leukemia which showed many phases of mitosis in the peripheral blood stream. This author calls attention to a characteristic indentation at the distal pole of the chromatin masses and to the fine ground glass appearance of the cytoplasm. Previous to these reports, mitotic leukoblasts have rarely received definite recognition in the peripheral blood. They merit recognition and closer study.

The following case of acute leukemia is reported because it showed many beautiful examples of the type of mitotic cells described by Groat and others. Dr Groat has examined the stained blood smears from the following case and agrees to their classification as mitotic leukoblasts, as well as the suggestion that the cells are probably lymphoblastic in origin.

*Case Report* P. H., a white male aged two years, eleven months, was first seen September 20, 1930. The complaint was an illness of four weeks duration, characterized by an onset with acute tonsillitis and high fever for two weeks and then irregular fever and enlargement of the cervical lymph glands and anemia.

The family history was unimportant. There were five brothers and two sisters living and well.

The patient had had a normal infancy and no illness except mild uncomplicated chicken pox at the age of two years.

On first examination there was marked pallor and a temperature of 104 degrees F by rectum. The tonsils were very large and red but free from ulceration and exudate. A small anterior cervical lymph gland was palpable on the right, on the left a discrete firm tender gland about 7 cm in diameter was noted. The spleen and liver were not palpable and the remainder of the examination yielded normal findings. The child was next seen two weeks later. Except for increasing pallor the patient had improved and there had been marked regression in the size of the cervical glands. A firm spleen was palpable about 7 cm below the costal margin. Several small furuncle-like lesions were present over the face and forehead. Three weeks later, the spleen and liver extended downward as far as the umbilicus, there had been a return of fever, and petechiae were present over the arms, trunk and legs. There was oozing of blood from fissures in the lips. The cervical glands were barely palpable. The patient was admitted to the Henrietta Eggleston Memorial Hospital for treatment and transfusions. From this time there was fluctuation in the size of liver, spleen and cervical glands. Throughout the illness, the peripheral adenopathy was limit-

ed to the anterior cervical glands. During the course of the illness the patient developed bilateral suppurative otitis media, bronchopneumonia (accompanied by a leukocyte count of 2,200 of which 76 per cent were lymphocytes) with recovery and bilateral axillary abscesses which were treated by aspiration and incision. The patient died about fifteen weeks after the onset of symptoms, unfortunately he was not under our observation at this time and an autopsy was not obtained.

*Laboratory.* Repeated urine examinations gave normal findings. The blood Wassermann reaction was negative. A throat culture yielded a scant growth of streptococci. One blood culture remained sterile. Two clot blood cultures revealed a pleomorphic gram-positive bacillus resembling a diphtheroid. A culture from the pus of the axillary abscesses showed the presence of staphylococci. During the course of the illness the blood counts varied as follows: Erythrocytes 3,070,000 to 1,370,000, hemoglobin between 70 per cent and 20 per cent, leukocytes between 14,500 and 1,700. The differential leukocyte counts displayed a variation between 97 and 66 per cent lymphocytes. Eosinophiles were absent except on one occasion. Blood platelets were greatly reduced in number, one count yielded 35,000 platelets, mostly small forms. The



FIG 1 Two typical immature lymphocytes. One cell shows azure granules.

red blood cells showed marked achromia. Normoblasts and macronormoblasts were present. There was a rare mitotic erythroblast. Reticulocytes were almost absent. The typical immature leukocytes constituted about one half of the lymphocyte percentage. These cells were two or three times as large as an erythrocyte, the cytoplasm took a medium blue stain with Wright's stain and in some cells azure granules were present. The nuclei stained lilac to purple and showed a fine reticular

network with massing of the chromatin about the periphery of the nucleus to form a nuclear membrane. Many nuclei contained one or two pale nucleoli. An occasional cell contained two distinct nuclei and resembled figure 4 in the report by Bowcock and Bishop. Myelocytes were seldom seen. The clotting time was four minutes. The bleeding time was 19 minutes. Specimens of vomitus had a prune juice color and gave a strong chemical reaction for blood.

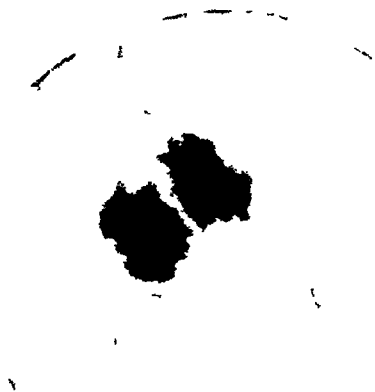


FIG 2 AND 3 Mitotic leukoblasts. The cytoplasm stained pale to medium blue and had a very fine ground glass appearance. The chromatin took a purple stain.

(The photomicrographs were made by the Photographic Department, College of Medicine, Syracuse University. Magnification 1100 X.)

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## Editorials

### *The Rôle of Syphilis in the Etiology of Angina Pectoris, Coronary Arteriosclerosis and Thrombosis and of Sudden Cardiac Death*

There is a tendency in recent American clinical papers on angina pectoris and coronary sclerosis to ascribe but little importance to the part played by syphilis in the production of these conditions. For instance, Levine believes that syphilis is only rarely an etiologic factor in the causation of coronary thrombosis. In only three of his eighty-nine cases in which a Wassermann reaction was made was there a positive reaction, and in only one other case with a negative reaction, was there a history of a primary sore. Therefore, it would appear that only 4.5 per cent of his patients were syphilitic, and it does not necessarily follow that the syphilis in the patients had any direct etiologic relationship to the coronary thrombosis. In only one of his patients, the youngest of his series (36 years), did this seem likely. Levine's criteria were, however, almost wholly clinical, and in a small proportion based upon gross pathologic appearances. As is generally recognized, in no other disease than syphilis are such criteria more misleading and likely to give inaccurate statistics as far as the actual incidence of a syphilitic infection is concerned. In only forty-six of Levine's cases was an autopsy performed,

and this fact in itself, weakens greatly his conclusions as to whether syphilis was or was not present. Further, had autopsies been done, and the material carefully studied microscopically, the percentage of syphilitics might have been greatly increased. Even if this were the case there would still be the question as to whether the syphilis played a primary or secondary rôle in the coronary pathology and this question could have been settled only by a thorough microscopical study. In the few American reports on coronary disease in which a more thorough consideration of the co-existence of syphilis was carried out, the percentage incidence of syphilis was found to be considerably higher than that found by Levine. In two out of thirteen cases dying of coronary disease, Stone found syphilitic periarteritis of the coronaries (16 per cent), and in eighty-six autopsies of coronary sclerosis, Willis and Brown found syphilis of the aorta in nineteen per cent. In recent papers written on the continent, there is shown a disposition to ascribe to syphilis a more important rôle in the production of coronary sclerosis and thrombosis than that accorded it by American observers. At the University of Michigan, we have approached this problem from the standpoint of the autopsy and the microscopic demonstration of the lesions of latent syphilis, checking up

the incidence of angina pectoris, coronary sclerosis and thrombosis, myocardial infarction, myocardial fibrosis, due to interstitial myocarditis and sudden cardiac death, both in cases showing evidences of latent syphilis and in those showing no such evidence. In the twenty years, 1909 to 1929, there were in the Pathological Laboratory of the University of Michigan, 1675 autopsies on individuals over twenty-five years of age. Of this number there were 408 males and 86 females that showed the microscopic lesions of active latent syphilis. These lesions are characteristic perivascular infiltrations of lymphocytes and plasma cells, in which *spirocheta pallida* has been demonstrated so frequently (in about fifty per cent of cases), as to make them pathognomonic for syphilis. These lesions showed their highest incidence in the aorta, in 97.6 per cent of cases for the first decade, 1909-19, in 86.3 per cent for the second decade 1919-1929. As far as the heart and coronary vessels were concerned the microscopical study showed the following. In 169 cases of syphilis (1909-1919) there were 53 cases of coronary sclerosis without thrombosis, 9 cases of syphilitic disease of the coronaries, 1 case of coronary thrombosis and sclerosis and no case with a clinical history of angina pectoris. In this same decade, out of the 169 cases of syphilis, there were 13 cases of sudden cardiac death. None of the latter showed coronary sclerosis without evidence of syphilitic disease of these vessels; but the myocardium of these cases presented the picture of a diffuse syphilitic myocarditis. In 4 cases only was there a microscopic picture of

myocardial infarction. In the decade, 1919-29, there were 332 cases giving microscopical evidence of syphilis. Of this group 172 showed coronary sclerosis and 55 showed syphilitic disease of the coronaries, including 1 case of gummatous coronary arteritis. In this same group, there were 5 cases of coronary thrombosis, 4 of these were associated with coronary sclerosis alone, and only 1 with syphilis of the coronary. There were 6 cases of angina pectoris in this group, 5 showing coronary sclerosis alone, and only 1 showing coronary syphilis. The syphilitic group for this decade showed 25 cases of sudden cardiac death, in 13 of these the coronaries showed arteriosclerosis alone, in 12 cases the coronaries showed syphilitic lesions, and six of these showed both syphilis and sclerosis. Eleven of the cases of sudden death showed evidences of myocardial infarction, 14 showed no infarction, but the picture of a chronic diffuse interstitial myocarditis of syphilitic type. Five of the cases of myocardial infarction were associated with occlusion due to coronary sclerosis alone, 6 were associated with both sclerosis and lesions of syphilis. Comparing the non-syphilitic autopsies of the same two decades we find that in 1909-19 the percentage of cases showing coronary sclerosis was 24, that of angina pectoris was 0.46, that of myocardial infarction was 0.46, and that of coronary thrombosis was 0.46. In the second decade the percentage of coronary sclerosis was 38, that of angina was 0.53, of myocardial infarction 0.74, and of coronary thrombosis 0.74. In the syphilitic autopsies for 1919-19, the percentage of coronary sclerosis

was 31+, that of angina 0, that of myocardial infarction 24, of coronary thrombosis 058. In the second decade (1919-29) the syphilitic group showed a percentage of coronary sclerosis of 52, angina 18, myocardial infarction 33, and coronary thrombosis 15. This is the only study ever made in which microscopical criteria were employed as foundation for the presence or absence of syphilis. Extending over a period of 20 years it offers most valuable information concerning the relation of coronary sclerosis, angina pectoris, coronary thrombosis, and myocardial infarction, and demonstrates conclusively that these conditions have a higher rate of incidence in the syphilitic cases than in the non-syphilitic. This study also shows that active syphilitic lesions are infrequent in the larger coronary branches, and that they rarely produce occlusion of the vessels, or lead to thrombosis or myocardial infarction. Syphilis, therefore, must predispose secondarily to coronary sclerosis and its resultant pathology. Of still greater importance is the relation of sudden cardiac death to syphilis. In our cases, extending over two decades, sudden death due to cardiac decompensation and dilatation was almost five times as frequent in the latent syphilitics as in the non-syphilitics. This bears out the writer's contention as to the importance of cardiac involvement as a frequent cause of death in the syphilitic. Syphilis acts both primarily and secondarily upon the heart. As a primary factor it produces myocardial insufficiency through the slow production of fibrosis due to interstitial myocarditis. Twenty-three of our cases of sudden death showed

this lesion alone. Valvular lesions were not present in any one of these cases. As a secondary factor, syphilis plays a large rôle in the production of aortic and coronary sclerosis, which in turn may lead to coronary occlusion, thrombosis, and myocardial infarction. The published statistics of the larger insurance companies constantly call attention to the increasing incidence of cardiac deaths in the population at large, and much talk has resulted as to the necessity of educating the people along lines of prevention of cardiac disease. But in all of this propaganda there is no word of the importance of syphilis as an etiological factor in the cardiac deaths of middle age and early old age. And the insurance companies go on insuring the clinically cured latent syphilitic as considerably as if he had never had syphilis. Rheumatic fever reaps its harvest of cardiac deaths from valvular lesions, usually before middle life. Syphilis takes its toll at middle life and in early old age; for syphilis produces premature old age of the heart, that is all that it amounts to, early fibrosis and atrophy, early cardiac inadequacy, premature cardiac death. The increase of cardiac deaths in our older groups is, therefore, due chiefly to premature cardiac old age, and one of the most important factors causing this is syphilis. Further, the longer the population survives, the greater the number of cardiac deaths there will be, and with the increase in expectancy of life that has already been brought about, we must expect a great increase in the number of cardiac deaths, for cardiac death is the normal death of uncomplicated old age.

*The Presence of Heavy Metals in Human Gallstones.*

As early as 1883, Hoppe-Seyler found copper and iron in pigment stones; but his observation excited no interest, and has apparently been forgotten until very recently, when A. F. Peel reported the presence of copper in pigment- and cholesterol-pigment-calcium stones. He found that the ash of these calculi is black, and when dissolved in acids, and ammonia added, an intense blue color is produced, thus indicating the presence of copper. In Hammarsten's textbook of physiological chemistry the statement is made that copper and iron are found in pigment stones. Up to the present time, however, quantitative estimations and comparative studies of different forms of gallstones as to their metal content have never been carried out. It was not until Schonheimer and Oshima had worked out an exact method for the determination of copper, that the normal copper content of human tissues could be estimated. It has long been known that copper is a constant constituent of living tissues; but its exact determination has hitherto been found impossible, owing to the great variations in results obtained by various methods, particularly as the majority of these were macro-methods requiring for a single estimation several hundred grams of ash. All workers in this line are agreed that the concentration of copper in all organs is very slight, and that at most only a few milligrammes per kilo are present in an organ. The greatest copper-content has been found in the liver; in the normal liver this ranges from about 20-35 mg per kilo. In certain diseases the

hepatic copper content may be greatly increased; this is true of practically all forms of cirrhosis. In other organs no similar concentration of copper content has been found to occur in any known disease. This finding, which has been confirmed by Oshima and Schonheimer, Askanazy, Schonheimer and Herkel, Cherbuliez and Ansbacher, is significant in fixing the liver as the one organ chiefly concerned in the metabolism of copper. The presence of high copper contents of the liver in different forms of cirrhosis throws a sidelight on Mallory's contention of copper poisoning as a cause of hemachromatosis. For if a high copper content is characteristic of all forms of cirrhosis, its significance may be simply that of copper retention, and not that of exposure to toxic doses of copper. The association of a toxic condition with these high copper contents of the liver remains yet to be proved. It is now settled that copper is a regular constituent of all gallstones, except the so-called pure cholesterol stones, possessing a chemically scarcely recognizable organic ground-substance. Quantitative analyses show that the cholesterol-free ground-substance of all other forms of gallstones contain large amounts of copper. The dark pigment and calcium residue left after extraction of cholesterol-pigment-calcium stones with ether contains 0.3-1 per cent of copper; and the same amount of copper may be found in pure pigment stones not extracted by ether. Copper is present also in the earthy pigment and carbonate stones. In gallstones the copper concentration reaches a height greater than that found in any other organ. While in the normal liver

the copper content is about 35 mg per kilo, in gallstones it may reach 10,000 mg per kilo. It is quite evident from this that copper must be considered an element entering into the body metabolism, and the physiology and pathology of copper metabolism constitutes at the present a totally unexplored field. Schonheimer and Herkel (*Klin Wchschr*, February 1, 1931) have investigated the occurrence of other metals in gallstones besides copper. Zinc, which possesses similar biologic properties to those of copper, is also a regular constituent of body tissues, especially of the liver. In this organ the regular content of zinc is about double that of copper, running about 40.5 per cent per kilo of fresh liver, and 180 mg per kilo of dried liver. There is, however, no exact method of micro-analysis of zinc. The authors' estimations of zinc in gallstones have, therefore, only the value of relative determinations. Their investigations show, nevertheless, a concentration of zinc in gallstones, which is higher than the organ-concentration, but is not so significant as that of cop-

per. A third heavy metal, studied as to its presence in gallstones, was manganese. This metal occurs in the organs in so small amount that it can be demonstrated only by means of the most sensitive methods. In extracted gallstones it was found to occur in a concentration of about 5 mg per kilo. While this amount is very small, it is relatively high as compared to the normal manganese content of the organs and tissues. Of other heavy metals, iron was found in gallstones in a concentration of 0.1-0.2 per cent; a concentration which is relatively higher than the iron content, not found in hemoglobin, of the organs. All four heavy metals, copper, zinc, manganese, and iron, are, therefore, increased in gallstones. In relation to the liver, this increase in copper-content is the most significant, that of the zinc content is the least. As to the biologic significance of this relatively rich content of the four heavy metals in gallstones, nothing can as yet be offered and this problem is intimately bound up with that of the formation of gallstones.



## Abstracts

*Chronic Typhoid Cholecystitis* By TRACY B MALLORY and GEORGE M LAWSON, JR.  
(Am Jour Path, January, 1931, p 71)

In spite of the extensive literature dealing with the bacteriological and epidemiological features of typhoid cholecystitis, Mallory and Lawson found but three publications with adequate descriptions of the histological picture of this condition. A series of seven cholecystectomies in known typhoid carriers afforded an opportunity for a more complete study than had been accomplished previously. In these seven cases of known pure typhoidal infection the gall bladder contained in each instance, pale, mucoid, clear to moderately turbid, colorless to light yellowish green staining bile. Normal bile was not recovered. Stones were found in all but one case and in one instance *Bact typhosus* was recovered from the center of a stone. The microscopical picture presented certain constant features. In all cases an inflammatory infiltration was present, always most marked in the mucous membrane, which was considerably thickened by a diffuse infiltration of lymphocytes and plasma cells, chiefly the former. Dense focal clusters of lymphocytes in lymph nodule formation with hyperplastic germinal centers were found in every instance. These averaged three to four in each microscopical section and occurred in approximately equal numbers in all portions of the wall from neck to fundus. A survey of four hundred routine slides of chronic cholecystitis showed similar lesions in 65 per cent of the cases and analysis of the clinical histories of this group showed these changes to be five times as common in cases with positive histories of typhoid fever as in cases with negative histories. The investigators conclude that the lesion described is characteristic of chronic typhoid cholecystitis but is not pathognomonic.

*The Medical Care of the Cancer Patient* By HENRY JACKSON, JR, and GEORGE R MINOR (The American Journal of Cancer, January, 1931, p 6)

This short, compactly written paper is intended to present the present day responsibilities of the internist to the patient upon whom a diagnosis of cancer has already been made, as well as to indicate certain preventive measures which fall within the province of the general practitioner. The wise physician guards his patients as far as possible against chronic irritation, and such possible etiological factors as infected antra, decayed and carious teeth, ill-fitting dental plates, chronic inflammatory lesions of cutaneous and mucosal surfaces, cervical lacerations, "lumps" in lymph-node areas, breast, sub-cutaneous tissues and muscles, may all properly receive attention. The possibility of early diagnosis rests largely with the patient himself. He only is aware of his symptoms and can bring them to the attention of the physician, but the physician must study each and every patient completely. Skillfully performed periodic health examinations and attention to symptoms and signs, no matter how trivial they may appear, increase the opportunity for diagnosis in the incipient stage. Once malignant disease is diagnosed, there should be no tendency to temporize. Even when "nothing more can be done" in the curative sense, much can still be accomplished to maintain the morale of the patient, relieve his pain and improve his general condition. An attitude of cheerfulness and hopefulness on the part of those in attendance, sunlight, especially in the open air, and such physical activity as can be tolerated without fatigue, are important factors. Dietary requirements, both as to amount and character, should be prescribed in detail. For instance, in considerable care of the stomach the diet

finely ground liver and milk to which have been added concentrates of vitamins, together with other liquid foods, will often restore the patient to a comparatively comfortable state. Anemia can be lessened by appropriate therapy. Large doses of iron, as iron and ammonium citrate (U S P), from 4 to 6 grams daily, can cause anemia due to chronic blood loss to decrease rapidly. Whole liver (200 grams a day) will be found effective in certain cases and may be of great value when combined with iron therapy. Therapy is of little value when anemia is due to sepsis. This is best combated by overcoming the infection, if this be possible. Transfusion of blood may be used as an emergency measure in patients who are extremely anemic but iron and liver therapy can cause a more profound and lasting regeneration of blood. While many cancer patients come sooner or later to the use of morphine for relief of pain, it is found that careful management will render unnecessary the use of this drug in most instances. In a group of 90 patients, 10 of whom were receiving morphine previously, small doses of codeine and aspirin sufficed in every case to alleviate pain after proper care had been taken of the patient.

*Vaccinal Encephalitis* By HENRY R. VIETS and SHIELDS WARREN (The New England Journal of Medicine, March, 1931, p 475)

The cerebrospinal complications of anti-smallpox vaccination have now been reported in sufficient numbers to designate the syndrome definitely as vaccinal (or post-vaccinal) encephalitis. This disease was first

reported by Lucksch from Czechoslovakia in 1924, although it had been studied by Turnbull and McIntosh as early as 1912. Three examples, two with post mortem examination, are added in the paper under review to the brief list found in American literature. The most striking clinical feature of these cases, in conformity with those published by others, is the uniformity of the onset, course and other time relations of the symptoms. The first patient became ill on the twelfth day after vaccination and died on the fourteenth day. The second case was mild and non-fatal, with onset on the eleventh day after vaccination. The third patient had his first symptoms on the tenth day and died on the fourteenth day after vaccination. The early symptoms are headache, vomiting and pyrexia, with a tendency toward paralysis, consisting of weakness of the cranial nerves or of the extremities. In infants, convulsions are frequent. Consciousness is soon lost. Sphincter control is usually affected, incontinence being common. The occurrence of trismus may lead to an erroneous diagnosis of tetanus and tetanus antitoxin has been administered under the assumption that the disease was atypical tetanus. The mortality rate is high, from 35 to 50 per cent in reported series. If recovery takes place, it tends to be complete, without residual defect. The principal histopathological lesions in those cases which die are perivascular cellular infiltration and demyelination, most intense in the pons and medulla but also widespread throughout the brain. The authors believe that these changes are distinguishable from those found in encephalitis lethargica or poliomyelitis.

## Reviews

*A Practical Medical Dictionary* By THOMAS LATEROPE STEDMAN, A. M., M. D., Editor of the "Twentieth Century Practice of Medicine," and of the "Reference Handbook of the Medical Sciences," formerly Editor of the "Medical Record." Eleventh, Revised Edition. Illustrated. William Wood and Company, New York, 1930. Price in Cloth, \$7.50 net.

This edition has been thoroughly revised, and a large number of new titles introduced, made necessary by the somewhat accelerated movement of medicine during the last two years. Particularly in Bacteriology have the changes in nomenclature been very extensive, so that an entire revision of this subject has been found necessary. All the names proposed by the Committee on Nomenclature of the American Bacteriological Society have been incorporated with cross-references to and from the older and more commonly employed terms. Definitions of words recently introduced into the physics of radiology have also been included. A number of new plates have been inserted, adding to the usefulness of the book as a work of reference. Altogether this dictionary offers a very complete survey of the medical terminology of the day. It lacks, however, something which would greatly increase its usefulness to medical writers, and especially to medical editors, and that is syllable division. This is shown in only a relatively small number of the terms given. The editor of this work has accomplished much for American medicine in his insistence upon the purification of medical orthography. For two decades he has insisted upon the correct spelling of the alkaloids, and the use of *c* instead of *k*, in words derived from the Greek through the Latin, in spite of the bad example set by the Journal of the American Medical Association. He has had the satisfaction of seeing the present editor of the Journal restore the final *c* to the alkaloids

and chemical bases, and conform at last to the standards of correct spelling. This has certainly been worth twenty years of waiting, and Dr. Stedman may be congratulated on his long fight for accuracy, and for preserving American medical terminology from the threatened degradation. Every student and every medical practitioner must have a medical dictionary, and we can recommend this one.

*A Textbook of Surgery* By JOHN HOMANS, M. D., Assistant Professor of Surgery in the Harvard Medical School. Compiled from lectures and other writings of twenty-three members of the Surgical Department of the Harvard Medical School. Illustrated. Charles C. Thomas, Springfield, Illinois, 1931. Price, \$9.00, postpaid.

The aim of this book is to record and amplify lectures now given by members of the surgical department of the Harvard Medical School, to reinforce this material with historical information and illustrations and thus to put forth a book, which, within the limits imposed by a single volume, is intended to teach the fundamentals and something of the practice of surgery. Its 1,200 pages are divided into fifty-six chapters of which the first ten deal with general subjects and etiological agents. Repair, Surgical Bacteriology, Surgical Technique, Suppurative Inflammation, Ulcer and Gangrene and Their Causes, Trauma, Miscellaneous Infections, Tuberculosis, Syphilis, Tumors and Cysts. The remaining chapters deal with the surgery of organs, systems and regions, including also those frequently omitted from general textbooks such as the eye, ear, nose and female generative tract. With this wide range of subject matter there is no opportunity for detailed treatment but, in general, the subject matter can be considered adequate for a textbook dealing

with fundamental considerations. As such it should be of great value to the medical student and to the practitioner desirous of reviewing the principles of surgical pathology. Perhaps because this book is a compilation from so many sources there are certain important omissions. For instance, fat embolism cannot be found by name in the index under fat, embolism, lung, fracture or lipemia, nor is it mentioned in the text in the section on pulmonary embolism. Under the caption 'Gangrene Due to Arterial Embolism and Thrombosis' there occurs the brief statement that in fractures, fat embolism *may perhaps* occur. In view of the widespread adoption of the Kahn test it is unfortunate that in the chapter on syphilis the Wassermann Reaction is discussed to the extent of nearly a page while the Kahn procedure is only mentioned by name in a list of other tests. There are three especially interesting features in this

book. One of these is the introduction of much historical material written in a vivid and pleasing style. Likewise the illustrations are unique in that with very few exceptions the 513 text figures are pen and ink line drawings which have been successfully reproduced on a thin uncoated paper. These are largely the work of Mr Willard C Shepard. Many have the simplicity and artistic value of woodcuts, yet vividly portray the character of the lesions illustrated. This method of illustration proves inadequate, however, for the few histo-pathological illustrations which are introduced. Finally, the body of the text is followed by a Bibliographical Index of forty-six pages which is a storehouse of references and eponyms of significance in the history of surgery. It is gratifying that a work intended primarily as a fundamental textbook should embody so much that is of cultural value in Medicine.

# College News Notes

## BALTIMORE CLINICAL SESSION

The Fifteenth Annual Clinical Session of the American College of Physicians, held at Baltimore, Md, March 23-27, with an additional day at Washington, D C, on March 28, was the most largely attended Session the College has ever conducted, the total attendance being 2,043. Of this number, however, 204 were visiting ladies, members of the families of attending physicians, but the official registration without the visiting ladies, 1,839, compares with 1,296 at the previous Session in Minneapolis during February, 1930. At Baltimore, there were physicians present from every State of the United States, with the exception of Nevada. Naturally, the attendance for Maryland was highest, with a total of 609, New York was second with 204, Pennsylvania third with 163, the District of Columbia fourth with 135, New Jersey fifth with 84, Ohio sixth with 74, Massachusetts seventh with 52, and Illinois and Michigan tied for eighth place with 47. It is interesting to note that 1,664 were from East of the Mississippi, 153 West of the Mississippi, and 22 from Canada. At the Minneapolis Clinical Session, during February, 1930, the attendance was 657 from West of the Mississippi and 634 East of the Mississippi, with but 5 attendants from Canada. These statistics are interesting when attempting to contemplate the attendance at the 1932 Clinical Session in San Francisco. The State of California ranks third in the number of members in the American College of Physicians, with 140 Fellows, 34 Associates, or a total of 174. Washington and Oregon both have a fair number of members, so that the three Pacific Coast States have a very adequate nucleus for arranging the next Clinical Session.

The scientific papers and a few of the more important clinics held in connection with the Baltimore Session will be printed in later issues of the Annals.

## PROCEEDINGS OF THE BOARD OF GOVERNORS

Thirty-five members of the Board of Governors, including Doctors Lee Wright Roe (Alabama), W. Warner Watkins (Arizona), Turner Zeigler Cason (Florida), Ernest B Bradley (Kentucky), Edwin W Gehring (Maine), Harvey Beck (Maryland), G. W. F Rembert (Mississippi), Louis H Fligman (Montana), Harlow Brooks (New York), T. Homer Coffen (Oregon), Clarence M Grigsby (Texas), Egerton L Crispin (California), Josiah N Hall (Colorado), Henry F Stoll (Connecticut), William Gerry Morgan (District of Columbia), Ernest E Laubugh (Idaho), Samuel E Munson (Illinois), Roscoe H. Beezon (Indiana), Thomas T Holt (Kansas), Roger I Lee (Massachusetts), Adolph Sachs (Nebraska), Leander A Riley (Oklahoma), Edward J G Beardsley (Pennsylvania), Edwin B McCready (Pennsylvania), G G Richards (Utah), Charles G Jennings (Michigan), A. Cornueo Griffith (Missouri), W Blair Stewart (New Jersey), Charles H Cocke (North Carolina), Julius O Aronson (North Dakota), Robert Wilson, Jr (South Carolina), Clarence H Beecher (Vermont), J Morrison Hutcheson (Virginia), John N Simpson (West Virginia), D Selater Lewis (Quebec), attended the Clinical Session and the meetings of the Board of Governors on March 23 and March 25.

Dr. W. Blair Stewart, of Atlantic City, N. J., presided as Chairman during the meetings of the Board. Dr. Stewart addressed the Board at length upon the functions of the Government in the various states, and presented for discussion many matters relating to the endowment of each state, the jurisdiction of Governors, the term of Governorship, etc.

Dr Ernest B Bradley, of Lexington, Ky, Vice Chairman of the Board of Governors, addressed the Board briefly concerning his duties as a member of the Committee on Credentials, emphasizing the fact that no physician should be recommended for election to Associateship unless his credentials and personal caliber are such as to practically guarantee his election to full Fellowship within the period of three to five years, as prescribed by the By-Laws

Dr Sydney R Miller, retiring President of the College, addressed the Board, stressing the importance of Governorships of the various states and territories, emphasizing that quality rather than quantity is the future aim of the College, and pointing out that complete co-operation with the Committee on Credentials is necessary for the proper selection of future members Dr Miller further pointed out that after December 31, 1931, all new members must enter first as Associates In his closing remarks, Dr Miller expressed the hope that the American College of Physicians will never change the present form of Annual Clinical Session to sectional meetings

Dr S Marx White, incoming President, also addressed the Board of Governors, corroborating the statements of Dr Miller, and stressing particularly the necessary co-operation which must exist between members of the Board of Governors and the Committee on Credentials Dr White also reiterated the thought that the present type of Clinical Session is the most beneficial form of meeting the College can conduct

Dr William Gerry Morgan, of Washington, Governor of the College for the District of Columbia, and President of the American Medical Association, addressed the Board briefly concerning the selection of future candidates He expressed the opinion that a physician should be recommended for election solely on the qualifications, personal and professional, he offers, that the qualifications should be quite definitely defined and stringently applied

Dr Charles H Cocke, Vice Chairman of the Committee on Credentials for Associateship, presented the Committee's report Upon motion regularly moved, seconded and carried, the following resolution was adopted

RESOLVED, that the report of the Committee on Credentials be approved, recommending the following list of candidates to the Board of Regents for election to Associateship (the list of 102 names appears on following pages, in connection with their final election by the Board of Regents)

Dr Clement R Jones, of Pittsburgh, Treasurer of the College, summarized the financial reports of the Treasurer and the Executive Secretary, the complete copy of which will appear later

Mr E R Loveland, of Philadelphia, Executive Secretary of the College, presented an annual report, salient points of which will be found under the proceedings of the General Business Meeting of the College on following pages The Executive Secretary presented the complete list of delinquent members of two years or more standing to the Board of Governors, with the request that he be notified immediately by the Governor of any delinquent member's state if there be any reason why said member should not be dropped from the College rolls, in accordance with the provisions of the By-Laws and the action of the Board of Regents

Dr Egerton L Crispin, of Los Angeles, Governor of the College for Lower California, extended an invitation for the 1932 Clinical Session to be held in San Francisco, enumerating the educational and entertainment facilities of his State This invitation was extended during a discussion regarding invitations from various cities that were to be presented to the Board of Regents

Dr Edwin W Gehring, of Portland, Governor for Maine, presented for discussion the opinion that the true purpose and significance of the American College of Physicians should be clarified to the public at large.

## PROCEEDINGS OF THE BOARD OF REGENTS

Meetings of the Board of Regents were attended by every Officer and every member of the Board of Regents, with the exception of Dr Aldred Scott Warthin and Dr John A. Lichty, First and Second Vice Presidents respectively, who were prevented from attendance at the meetings by illness, but both of whom were present in Baltimore. The detailed Minutes of the Board of Regents are too voluminous for publication here, but the most important items follow.

At their first meeting, March 22, the following list of 192 physicians were elected to Fellowship:

Frank Marberry Acree, Jr	Greenville, Miss
Harold Lindsay Amoss	Durham, N C
Walter Marion Anderson	San Diego, Calif
Edwin Cowles Andrus	Baltimore, Md
Ernest John Aten	Ambridge, Pa
Carroll Royer Baker	Washington, D C
Byron Fuller Barker	Bath, Maine
Nelson Waite Barker	Rochester, Minn
Charles Joseph Bartlett	New Haven, Conn
Frank Herbert Bartlett, Jr	Muskegon, Mich
Theodore Irving Bauer	Lansing, Mich
Richard Hugh McDowell Bayley	Lafayette, Ind
Julien Emil Benjamin	Cincinnati, Ohio
John Terrell Bennett	San Pedro, Calif
Harold Vincent Bickmore	Portland, Maine
Ivar Wessel Birkeland	Rochester, Minn
Wayne William Bissell	New Castle, Pa
Harry Bloch	Elizabeth, N J
Charles Sidney Bluemel	Denver, Colo
William Charles Boeck	Rochester, Minn
Clarence Henry Boswell	Rockford, Ill
Howard Boyd	South Manchester, Conn
Harry A Brandes	Bismarck, N D
Orville Harry Brown	Phoenix, Ariz
Philip Walling Brown	Rochester, Minn
Herbert L. Bryans	Pensacola, Fla
Thomas Cayigas	Washington, D C
George Wehnes Calver	Washington, D C
Manley Joseph Capron	Battle Creek, Mich
Harry Wardwell Carey	Troy, N Y
Martin Grover Carter	Los Angeles, Calif
Arthur Raymond Cault	Elizabeth, N J
William Bessie Castle	Boston, Mass
Ross McClure Chapman	Towson, Md
Henry Leonard Childerine	New York, N Y
Harry A. Collins	Des Moines, Iowa
Paul Henry Connor	Denver, Colo
John Hamilton Crawford	Brooklyn, N Y
Samuel Leslie Cross	Asheville, N C
John Henry Crompton	New York, N Y
William Walter Crompton	New York, N Y
John Henry Crompton	Washington, D C
William Walter Crompton	Lafayette, N J

Arthur Bliss Dayton  
 Harold Comonfort Denman  
 Oswald Evans Denney  
 Wilfred Sidney Dennis  
 Charles Knight Deyo  
 Karl Herman Doege  
 Walter Foster Donaldson  
 Julius P Dworetzky  
 Frederick Eigenberger  
 Mary Josephine Erickson  
 Theodore Schlosser Evans  
 Frederick Fahlen  
 Louis Sanders Faust  
 Robert Lee Felts  
 Clinton Durham Fife  
 Clement Carl Fihe  
 Seymour Fiske  
 Harry Ernest Flansburg  
 George Beard Fletcher  
 Lewis Barr Flinn  
 Claude Ellis Forkner  
 James A Fountain  
 William Wellington Fox  
 Frederick Olaf Fredrickson  
 William Louis Freyhof  
 Alfred Friedlander  
 Erwin Deaterly Funk.  
 William Harris Funk  
 Levi Harrison Fuson  
 Adolph Stephen Gabor  
 George Howard Gehrmann  
 Walter Albert Gekler  
 William Wellington George  
 Isaac Gerber.  
 Earl Rudolph Gernert  
 George Burton Gilbert  
 Joseph LeRoy Gilbert  
 Archie Leland Gleason  
 Ben Ely Grant  
 Charles Marion Griffith  
 Samuel Bernard Hadden  
 William W Hall  
 John Ralph Hamel  
 Hans Hansen  
 George Argale Harrop, Jr  
 Lawton Mervale Hartman, Jr  
 William Gettier Herrmann  
 Theophil James Holke  
 Maynard Edward Holmes  
 Harold Phillips Hook  
 Tasker Howard  
 William Stumpson Hubbard

New Haven, Conn  
 Brooklyn, N Y  
 Carville, La.  
 Denver, Colo  
 Poughkeepsie, N Y  
 Marshfield, Wis  
 Pittsburgh, Pa  
 Liberty, N Y  
 Sheboygan, Wis  
 Thomasville, Ga  
 New Haven, Conn  
 Phoenix, Ariz  
 Rochester, Minn  
 Durham, N C  
 Dayton, Ohio  
 Cincinnati, Ohio  
 New York, N Y  
 Lincoln, Nebr  
 Hot Springs Nat'l Pk, Ark  
 Wilmington, Del  
 Belmont, Mass  
 Macon, Ga  
 Atlantic City, N J  
 Chicago, Ill  
 Cincinnati, Ohio  
 Cincinnati, Ohio  
 Wyomissing, Pa  
 Portsmouth, N H  
 St Joseph, Mo  
 Bethlehem, Pa  
 Wilmington, Del  
 Albuquerque, N M  
 West Palm Beach, Fla  
 Providence, R I  
 Louisville, Ky  
 Colorado Springs, Colo  
 Washington, D C  
 Great Falls, Mont  
 Glendale, Calif  
 Washington, D C  
 Philadelphia, Pa  
 Watertown, N Y  
 Portland, Maine  
 St Cloud, Minn  
 Baltimore, Md  
 York, Pa  
 Asbury Park, N J  
 Freeport, Ill  
 Syracuse, N Y  
 Pittsburgh, Pa  
 Brooklyn, N Y  
 Brooklyn, N Y



Ann Arbor, Mich  
New Brunswick, N J  
Springfield, Ohio  
New Orleans, La  
Baltimore, Md  
Boston, Mass  
Boston, Mass  
Newark, N J  
Hackensack, N J  
Holtsville, N Y  
Los Angeles, Calif  
Toledo, Ohio  
San Diego, Calif  
Baltimore, Md  
Elizabeth, N J  
Pittsburgh, Pa  
Baltimore, Md  
Toronto, Ontario, Can  
Pittsburgh, Kan  
Tampa, Fla  
Oklahoma City, Okla  
Baltimore, Md  
Las Cruces, N M  
Hamilton, Ontario, Can  
Cleveland, Ohio  
Buffalo, N Y  
Seattle, Wash  
Dallas, Texas  
Phoenix, Ariz  
Phoenix, Ariz  
Mount Airy, N C  
Hot Springs, S D  
University, Va  
Albuquerque, N M  
Grand Rapids, Mich  
Rochester, Minn  
Washington, D C  
Washington, D C  
Boston, Mass  
Philadelphia, Pa  
Minot, N D  
New York, N Y  
Jamaica, N Y  
Rochester, Minn  
Washington, D. C.  
Oscar's Mills, Pa  
Patuxent, Md  
Buffalo, N Y  
Harrisburg, Pa  
Harrisburg, Pa  
Portland, Tenn  
Wilmington, D C

Edward Harper Rynearson  
 Karl Schaffle  
 William Magill Schultz  
 John Alston Sevier  
 Blanton Page Seward  
 Arthur Anderson Shawkey  
 Paul Galpin Shipley  
 John Vincent Smith  
 Thomas Charles Smith  
 William Lester Smith  
 Otis Burgess Spalding  
 Ralph Stanley Stauffer  
 Amos Henry Stevens  
 Edward Julius Stieglitz  
 John William Stofer  
 George Franklin Stoney  
 Clifford John Straehley  
 Raymond Wooldridge Swinney  
 Joseph Gerard Terrence  
 Warren Thompson  
 Willard Owen Thompson  
 Walter Lewis Treadway  
 George Milton Underwood  
 Michael Vinciguerra  
 Walter Alfred Vogelsang  
 Fred Henry Voss  
 Charles William Wainwright  
 Andrew Wallhauser  
 Groesbeck Francis Walsh  
 Marine Ruffner Warden  
 William Virgil Watson  
 John Alexander Wentworth  
 Priscilla White  
 Ely Locke Whitehead  
 Otto George Wiedman  
 Franklin Davis Wilson  
 Edward I Wolfe  
 John Bloss Wolfe  
 Harold G Wolff  
 James Edwin Wood, Jr  
 George Jesse Wright  
 Harold Edson Wright  
 Walter Simrall Wyatt  
 Robert Morris Wylie  
 Wallace Mason Yater

Rochester, Minn  
 Asheville, N C  
 Tucson, Ariz  
 Colorado Springs, Colo  
 Roanoke, Va  
 Charleston, W Va  
 Baltimore, Md  
 Perth Amboy, N J  
 Battle Creek, Mich  
 Norfolk, Va  
 Washington, D C  
 Hagerstown, Md  
 Everettville, W Va  
 Chicago, Ill  
 Gallup, N M  
 Erie, Pa  
 Cincinnati, Ohio  
 Kansas City, Mo  
 Brooklyn, N Y  
 Omaha, Neb  
 Chicago, Ill  
 Washington, D C  
 Dallas, Texas  
 Elizabeth, N J  
 San Diego, Calif  
 Kingston, N Y  
 Baltimore, Md  
 Pittsburgh, Pa  
 Fairfield, Ala  
 Albuquerque, N M  
 Toronto, Ontario, Can  
 Hartford, Conn  
 Boston, Mass  
 San Diego, Calif  
 Hartford, Conn  
 Norfolk, Va  
 Forty Fort, Pa  
 Wilkes-Barre, Pa  
 Baltimore, Md  
 University, Va  
 Pittsburgh, Pa  
 Baltimore, Md  
 Lexington, Ky  
 Huntington, W Va  
 Washington, D C

The following resolution was regularly adopted

RESOLVED, that the Committee on Credentials be requested to go into the whole matter of the admission of candidates and the method by which information is secured, and that the Committee return a report of recommendations to the Regents at a subsequent meeting

The combined Financial Report of the Treasurer and the Executive Secretary was presented (This will be printed in the May issue)

Dr Clement R Jones, Treasurer, reported that the Finance Committee recommended that in addition to the \$8,400, which is already in the Endowment Fund of the College, \$41,600 be transferred in securities to the Endowment Fund, making a total of \$50,000, and that this \$50,000 become the nucleus of an Endowment Fund to be placed with a trust company, with the hope that in the near future \$250,000 could be accumulated, the income from which at 4% would be \$10,000 annually, to be spent on some appropriate purpose, perhaps some outstanding project connected with the practice of Internal Medicine in this country After general discussion, a resolution was regularly adopted, approving of the Treasurer's report, and adopting the recommendation of the Finance Committee

At the meeting of the Board of Regents on March 23, the resignations of the following were regularly accepted

William L Funkhouser (Fellow), Atlanta, Ga  
Paul G Weston (Fellow), Jamestown, N Y  
Walton Forest Dutton (Associate), Amarillo, Texas  
Edgar Webb Loomis (Associate), Dallas, Texas  
Louis K Patton (Associate) Amarillo, Texas  
Norman M Smith (Associate), Minneapolis, Minn  
William H Treible (Associate), York, Pa

Dr Daniel D. V. Stuart, of Washington, D C, was reinstated as a Fellow of the College

The following list of 102 candidates recommended by the Board of Governors were regularly elected to Associateship

Grant Orante Favorite  
 James Francis Finnegan  
 Robert Stanley Flinn  
 Leonard H Fredericks  
 Amos Carvel Gipson  
 Clark C Goss  
 William Edward Hall  
 Arthur Beck Hamilton  
 Andrew Harvey  
 Frank J Heck  
 John Mark Higgins  
 William Edward Hill  
 George McClintock Hutchison  
 Miletus Brown Jarman  
 William Nathan Jenkins  
 Clyde Reynolds Jensen  
 Earl Jones  
 Ferdinand Michael Jordan  
 Herbert T Kelly  
 Clapham Price King  
 Arthur Ruel Kintner  
 James Service Knowles  
 Chester M Kurtz  
 Glendon R Lewis  
 Dean W Marquis  
 Eugene Roland Marzullo  
 Orlando Benedict Mayer  
 Samuel James McClendon  
 Charles Harold McEnerney  
 Roy DeV Vaughan Metz  
 Edgar R Miller  
 Clarence D Moll  
 Harold W Palmer  
 Thomas M Palmer  
 Elbert Smith Parmenter  
 Frank Pearlstein  
 Roy G Pfozter  
 Virgil Guy Presson  
 Robert B Radl  
 Howell Sheppard Randolph  
 Hilton Shreve Read  
 James Seay Read  
 John Herbert Reading, Jr  
 Maurice L Ripp  
 John James Francis Rooney  
 Milford Owen Rouse  
 Howard A Rusk  
 Lutfi M Sa'di  
 Samuel B Scholz, Jr  
 Edward Henry Schwab  
 Lawrence Burton Sheldon  
 Judd Campbell Shellito

Philadelphia, Pa.  
 Tututula, Samoa  
 Phoenix, Ariz  
 Bismarck, N D.  
 Gadsden, Ala  
 Seattle, Wash,  
 Meriden, Conn  
 Bethlehem, Pa  
 New York, N Y  
 Rochester, Minn  
 Sayre, Pa  
 Naugatuck, Conn  
 Ridgway, Pa  
 Hot Springs, Va  
 Port Gibson, Miss  
 Seattle, Wash  
 Brownwood, Texas  
 Rochester, Minn  
 Philadelphia, Pa.  
 Washington, D C  
 Rochester, Minn  
 Millville, N J  
 Madison, Wis.  
 Syracuse, N Y  
 East Orange, N J  
 Brooklyn, N Y  
 Columbia, S C  
 San Diego, Calif  
 Washington, D C  
 Taylors, S C  
 Wilmington, Del  
 Detroit, Mich  
 Wichita, Kansas  
 Jacksonville, Fla  
 Ferndale, Mich  
 West New York, N J  
 Buffalo, N Y  
 Tucson, Ariz  
 Dickinson, N D  
 Phoenix, Ariz  
 Atlantic City, N J  
 Nashville, Tenn  
 Merion, Pa  
 Elizabeth, N J  
 Rochester, N. Y  
 Dallas, Texas  
 St. Louis, Mo  
 Detroit, Mich  
 Philadelphia, Pa  
 Galveston, Texas  
 Baltimore, Md  
 Independence, Ia

Samuel G Shepherd	Philadelphia, Pa
Hubert Herman Shook	Cincinnati, Ohio
Hildegard Catherine Germann Sinnock	Quincy, Ill
Walter Fox Smith	Watertown, N Y
James MacLaren Strang	Pittsburgh, Pa
Norman Strauss	New York, N. Y
Genaro Suarez	San Juan, P R
John A Sweeney	Philadelphia, Pa
Henry Meyer Tabachnick	Portland, Maine
Harold Lazarus Tonkin	Williamsport, Pa
John William Towey	Powers, Mich
Wilmot Charles Townsend	West Hartford, Conn
Herbert L Treusch	Atlanta, Ga
Thomas J Vischer	Philadelphia, Pa
Wilmarth Bradford Walker	Cornwall, Conn
Herbert V Weirauk	Columbus, Ohio
Clifford Grete Weston	Glen Ridge, N J.
Neil J Whalen	Detroit, Mich
George K Wharton	Rochester, Minn
Raeburn James Wharton	Johnson City, N Y.
George John Young	Morristown, N J

The following resolution revising the regulations for the John Phillips Memorial Prize was adopted

Resolved, that the Board of Regents herewith approves the following set of revised regulations governing the John Phillips Memorial Prize, as recommended by the Committee.

- "I (a) Interpretation of Internal Medicine—This term should include not only Clinical Science, but, in addition, all those subjects which have a direct bearing upon the advancement of Clinical Science,
- (b) The work upon which this is based must have been done in whole or in part in the United States or Canada
- "II Not less than two or more than three members of the Committee should be reappointed each year,

- "V (a) The announcement of the Prize-winner will be made not later than two months before the Annual Meeting of the College
- (b) The Executive Secretary shall inform the recipient of the Prize that the College would be pleased to defray his transportation expenses when he attends the Annual Meeting to receive the Prize'

Dr W Blair Stewart, in the absence of Major E E Hume, Chairman of the Committee on Academic Costume reported progress in their investigations, but asked more time in which to present a final recommendation for adoption of any special insignia in connection with academic costume for the American College of Physicians

The Board of Regents approved detailed budgets recommended by the Committee on Finance for the year 1931

The following report, presented by Dr O H Perry Pepper, Chairman of the Committee on Postgraduate Medical Instruction, was accepted and filed, and the Committee dismissed with thanks

'The present committee on Postgraduate Medical Instruction, composed of Dr Leonard M Murray, Dr John H Musser and Dr O H Perry Pepper, was appointed recently to carry on the work started in 1927 by a committee under the chairmanship of Dr Phillips

"The former committee made, by correspondence, a survey of the existing facilities for postgraduate instruction in Internal Medicine and its affiliated branches throughout the United States and Canada On February 28, 1928, they reported the results of this survey to the Regents and asked for a continuation of the committee Dr Phillips' untimely death ended the committee's activities

"In the intervening years there have been many changes and much growth in Postgraduate Medical Instruction so that the data of the former survey is now largely useless The present committee has therefore considered the whole subject anew and begs to report its conclusions as follows

- "1 The committee is unanimously of the opinion that it would be a serious mistake for the College to offer or organize postgraduate courses of any type The committee does not feel that such an activity would be a wise one for the college to embark upon
- "2 That it would also be a mistake for the College to repeat its survey of postgraduate medical instruction facilities or to attempt to keep itself accurately informed concerning all the many courses offered
- "3 The committee does feel that the College should be on record as favoring and encouraging proper postgraduate education in Internal Medicine
- "4 Beyond this the committee feels that it is difficult for the College to go, but the following suggestions are offered for the Regents' consideration, should they wish to pursue the matter further

"(a) The College might maintain in its central office a Directory of Postgraduate Medical Instruction facilities from which inquiries could be answered Such a Directory could be maintained in either of two ways—it might be no more than a source of information derived from circulars, catalogues, etc, or it might attempt to advise the inquirer To do this latter would at once plunge the College into the inspection and rating of the various postgraduate agencies throughout the country The committee is doubtful as to the wisdom of such a course If done, however, the initiative should surely be placed upon the agency offering the course

"(b) The Maintenance of a page or column in the Annals containing a listing of Postgraduate facilities, and the publication in the Annals of articles and editorials on the need and value of postgraduate medical instruction

- “(c) The occasional underwriting by the College of the expenses of prominent lecturers from abroad who would travel or lecture under the auspices of the College
- “(d) The occasional underwriting by the College of the expenses of a small group of prominent Fellows persuaded to visit under the auspices of the College one or more communities to fill the program of a local meeting This would not only be a form of postgraduate medical instruction activity, but also would be proper publicity for the college in districts where such is needed

“None of these suggestions are of such a character as to constitute a major activity of the College and the committee is not deceived as to their value”

At the meeting of the Board of Regents on March 25, invitations for the 1932 Clinical Session were presented from San Francisco, Kansas City and Buffalo By unanimous adoption, it was resolved that the invitation from San Francisco be accepted Dr William J Kerr, Professor of Medicine at the University of California Medical School, was unanimously selected as General Chairman of the Clinical Program President S Marx White, President-Elect Francis M Pottenger and Executive Secretary E R Loveland were authorized to proceed with all arrangement of details, headquarters, time of meeting, etc

Dr Jonathan C Meakins, Professor of Medicine at McGill University, Montreal, extended a tentative invitation for the College to meet in Montreal, presumably during the month of February in 1933

The terms of members of the Finance Committee, after drawing lots, were established as follows, for 1931

Charles F Martin, Montreal, Que	1 year
Charles G Jennings Detroit, Mich	2 years
James S McI ester, Birmingham, Ala	3 years
Francis M Pottenger, Monrovia Calif	4 years

At the meeting of the Board of Regents on March 27, the appointment of some new members of the Committee on the John Phillips Memorial Prize was left to the discretion of the President

Dr George E Brown, of Rochester, was appointed Chairman, with other appointments deferred

#### PROCEEDINGS OF THE GENERAL BUSINESS MEETING

President Sydney R Miller presided at the General Business Meeting of the American College of Physicians at Baltimore, March 26, 1931 After the abstracting of Minutes of the previous meeting, the Treasurer presented the financial report for the year 1930 The Executive Secretary presented his annual report, from which the following statistics are abstracted

Deaths of Members since the Minneapolis Clinical Session

34 Fellows

4 Associates

Resignations accepted since the Minneapolis Clinical Session

4 Fellows

10 Associates

27 Life Members (7 having been added since the Minneapolis Clinical Session)

366 Fellows and 102 Associates were elected since the Minneapolis Clinical Session in 1930

This brings the total membership of the College to the following figures, as of March 25, 1931

Fellows	2123
Masters	6
Associates	583
	<hr/>
TOTAL	2712

The following resolution, presented by Dr Alfred Stengel, as prepared by a special Committee was overwhelmingly adopted

"The enactment of laws by the United States Congress and many State legislatures has deprived the medical profession of its inherent and deputized rights to prescribe drugs and remedial measures in such quantity as it may deem necessary in treating the sick

"New laws and regulations have been and are now being forced upon medical men to such an extent that they can no longer be the judge of their own methods of treatment, but must bow to the prescribed forms of non-professional legislators and boards

"State medicine is gradually undermining the ancient and traditional rights of medical practice and if continued at its present rate, legitimate practice will soon be displaced by a commercial type of cults and advertised self methods of treatment by patent and proprietary medicines

"Recognizing these deplorable conditions, the American College of Physicians, met in regular assembly, recommends

"*First* That every legitimate effort be made to impress upon the members of Congress that unrestricted medical treatment of disease by properly licensed physicians should be granted and that they should not be penalized on account of the misuse of medical methods by a very small percentage of so-called medical and non-medical men Let the profession be its own judge of how it can best treat the sick, and properly penalize those who flagrantly abuse their licensed or unlicensed trust

"*Second* That the Fellows and Associates of the College must become more active in medical legislation and join with their State societies in an effort to repeal inimical State laws now in force and influence a higher type of medical methods for the future protection of the sick and those to whom their lives are entrusted"

Dr S Marx White, of Minneapolis, was inducted to office as President for 1931-32, whereupon he addressed the assembled Masters and Fellows briefly



Dr Alfred Stengel, Chairman of the Nominating Committee, presented the following report

"The Nominating Committee, in accordance with the By-Laws, submitted the following nominations for elective Officers thirty days in advance of the annual meeting, as published in the ANNALS OF INTERNAL MEDICINE

For President-Elect	Francis M Pottenger, Monrovia, Calif
1st Vice-President	Aldred Scott Warthin, Ann Arbor, Mich
2nd Vice President	Charles G Jennings, Detroit, Mich
3rd Vice President	John A Lichty, Clifton Springs, N Y

"The Nominating Committee now unanimously submits the following suggestions for nominations for the Board of Regents and the Board of Governors

*Board of Regents*

Term Expiring 1932

To fill the vacancy existing in this group—

James B Herrick	Chicago, Ill
	Term Expiring 1934
James S McLester	Birmingham, Ala
Jonathan C Meakins	Montreal, Que
James H Means	Boston, Mass
Sydney R Miller	Baltimore, Md
James Alex Miller	New York, N Y

*Board of Governors*

Term Expiring 1933

James D Bruce	MICHIGAN—Ann Arbor
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Term Expiring 1934

Fred Wilkerson	ALABAMA—Montgomery
W Warner Watkins	ARIZONA—Phoenix
Turner Zeigler Cason	FLORIDA—Jacksonville
Russell H Oppenheimer	GEORGIA—Atlanta
James G Carr	Northern ILLINOIS—Chicago
F B Bradley (Vice Chairman)	KENTUCKY—Lexington
Edwin W Gehring	MAINE—Portland
Henry M Thomas Jr	MARYLAND—Baltimore
G W F Rembert	MISSISSIPPI—Jackson
Louis H Fligman	MONTANA—Helena
LeRoy S Peters	NEW MEXICO—Albuquerque
Luther F Warren	Eastern NEW YORK—Brooklyn
A B Brower	OHIO—Dayton
T Homer Coffen	OREGON—Portland
Charles T Stone	TEXAS—Galveston
Rock Skovster	WISCONSIN—Wauwatosa
Charles Hunter	MANITOBA—Winnipeg Can

"Your Committee recommends that no appointments be made for the coming year for the States of Delaware and Nevada

Respectfully submitted

(Signed) ALFRED STENGEL

Chairman, Nominating Committee"

President White announced that the By-Laws provide that there may be additional nominations from the floor. The following resolution was regularly adopted:

RESOLVED, that nominations be closed, and that the report of the Nominating Committee above presented be accepted and the elections approved.

PROGRAM ANNOUNCED PAPERS NOT PERSONALLY DELIVERED  
at the  
BALTIMORE CLINICAL SESSION

The following papers were not personally delivered by the contributors as announced on the General Sessions Program of the Baltimore Clinical Session. The College greatly regrets that these papers were omitted and feels that the following explanations should be given. These papers, however, will be officially published during the coming year in the "Annals of Internal Medicine."

- (1) "Pneumococcosis: Clinical and X-Ray Aspects," paper number 7, Wednesday, March 25, 1931

Dr. H. R. M. Landis, of Philadelphia, the contributor, was absent due to illness, and was forbidden to appear by his physician, on account of severe laryngitis, which prevented him from any public address.

- (2) "Endo-Bronchial Manifestations of Pulmonary Disease: Observation on Bronchoscopic Diagnosis and Treatment," paper number 8, Wednesday, March 25, 1931

Dr. Gabriel Tucker, of Philadelphia, was present in Baltimore, prepared to present his paper. He failed to appear only because of a misapprehension as to the interpretation of the intermission period printed on the General Sessions Program, which he misconstrued in the sense of thinking that the intermission divided the Program into morning and afternoon sessions.

- (3) "The Management of Patients with Extreme and Atypical Hyperthyroidism," paper number 2, Thursday, March 26, 1931

Dr. Frank H. Lahey, of Boston, had prepared his paper and has turned it in for publication. His failure to appear was due to a lapse of memory as to the specific time the paper was scheduled, probably occasioned by fatigue as a result of extensive lectures elsewhere.

**GIFTS TO THE COLLEGE LIBRARY**

Acknowledgment is herewith made of the receipt of the following donations of reprints and books to the College Library of publications by members:

Dr. Joseph T. Beardwood, Jr. (Fellow), Philadelphia, Pa.

1 Reprint

"Right-sided Carotid Pulsation in Hypertension"

Dr. I. D. Bronfin (Fellow), Denver, Colo.

5 Reprints

"The Importance of Animal Inoculation with, and Culture of Sputum, Microscopically Negative for Tubercle Bacilli" (with Louisa T. Black, M.D.)

"Observations on Some Cardiac Lesions

Coincident with Pulmonary Tuberculosis" (with Saling Simon, M.D.)

"Phrenic Nerve Avulsion and its Value in the Treatment of Pulmonary Tuberculosis" (with C. F. Hegner, M.D.)

"The Preventorium Child"

"Electrocardiographic Studies in Artificial Pneumothorax—A Report on 110 Cases" (with Saling Simon, M.D., and Louisa T. Black, M.D.)

Dr. Grafton Tyler Brown (Fellow), Washington, D. C.

1 Reprint

"Linseed Meal Sensitization"

Dr. Curran Pope (Associate), Louisville, Ky.

1 Reprint

"A Case of Tabes Treated by Electro-thermic and other Physical Measures"  
 Dr Carl V Vischer (Fellow), Philadelphia, Pa  
 1 Reprint

"Chronic Arthritis" (with Edwin O Geckeler, M D)

Dr Richard M McKean (Fellow) and Dr Elwood A Sharp (Fellow), both of Detroit, presented a resume of Clinical investigations to the Detroit Academy of Medicine on January 26, entitled, "Modern Treatment of Pernicious and Secondary Anemias"

Dr John V Barrow (Fellow), Los Angeles, lectured before the County Medical Society (Ventura County, Calif), January 13, on the subject of "Human Intestinal Protozoa and Their Clinical Manifestations" The lecture was illustrated by moving pictures of the organisms

The same lecture was given before the San Bernardino County Medical Society on February 3

Dr Edward S Sledge (Fellow), Mobile, Ala, is Chief of the Medical Department of the Mobile City and County Hospital

Dr L Winfield Kohn (Fellow), New York City, is the author of "Diseases of the Digestive System" in Two Volumes, recently published by the F A Davis Company, of Philadelphia Dr Kohn has presented it as a practical treatise for physicians and students

The Baltimore Medical Club, of New York, held its annual dinner under the Presidency of Dr Kohn, at the Barbizon Plaza Hotel on Saturday evening February 14 Over one hundred physicians from Con-

Dr Tom Bentley Throckmorton (Fellow), Des Moines, is the author of an article entitled "Silas Weir Mitchell A Man of Medicine and Letters," which appeared in the February, 1931, issue of The Journal of the Iowa State Medical Society

Dr Curran Pope (Associate), Louisville Ky, delivered an address on the "Character of Abraham Lincoln" over the radiophone of WLAP at Louisville on February 12 Dr Pope spoke under the auspices of the National Security League of New York

Dr Harold S Davidson (Fellow), Atlantic City, N J, is the author of an article entitled "Recurring Postoperative Parotitis," which appeared in the February, 1931, issue of The Journal of the Medical Society of New Jersey

Dr Walter L Bierring (Fellow), Des Moines, delivered the annual lecture of Alpha Omega Alpha of the University of Illinois College of Medicine on February 18 Dr Bierring is the National President of A O A

Dr William Egbert Robertson (Fellow), Philadelphia, Professor of Medicine at Temple University, addressed the Berks County Medical Society, January 13, on "The Fringes of Medicine"

Dr O H Perry Pepper (Fellow), Professor of Clinical Medicine in the School of Medicine of the University of Pennsylvania delivered the sixth annual Scripps Metabolic Clinic Lecture at La Jolla, Calif January 8-10, to members of the San Diego County Medical Society

Dr Pepper also gave a Stanley Black Memorial Lecture at Pasadena, Calif January 12

Medical Association, January 10, on "Simultaneous Bilateral Collapse in Treatment of Tuberculosis"

Dr Julius H Hess (Fellow), Chicago, delivered an address on "Focal Infections of Childhood," February 15, before the Rock Island County Medical Society

Dr James H Hutton (Associate), Chicago, addressed the Vermilion County (Ill) Medical Society, February 3, on "Endocrine Disorders Occurring in General Medicine"

Dr Hutton also addressed the DeWitt County (Ill) Medical Society, February 11, on "Diagnosis and Treatment of Common Endocrine Disorders"

The following Fellows of the College were among speakers at the meeting of the Sioux Valley Medical Society (Iowa), January 20-21

Dr William W Duke, Kansas City—Allergy,  
Dr W McKim Marriott, St Louis—Care and Feeding of Infants and Children,  
Dr Frederick A Willis, Rochester, Minn—Treatment of Heart Failure

Dr Hyman I Goldstein (Associate), Camden, spoke before the Camden County, (N J) Medical Society, February 3, on "Streptococcus Faucitis with Erythema Nodosum and Erythema Multiforme Exudativum"

Dr Frank R Menne (Fellow), Portland, Ore, was elected President of the Oregon Pathological Society, which was recently organized by pathologists of the State Medical Society

Dr Harlow Brooks (Fellow), New York City, was one of the speakers at the annual "Heart Night" conducted by the Philadelphia County Medical Society on February

11 Dr Brooks' subject was "Angina Pectoris"

Dr Elmer L Severinghaus (Fellow), Madison, addressed the Marathon County (Wis) Medical Society, January 15, on "Menopausal Disturbances and Hyperthyroidism"

Dr Arthur D Dunn (Fellow), Omaha, and Dr William P Wherry, Omaha, addressed the Omaha-Douglas County Medical Society, January 27, on "Chronic Hyperplastic Maxillary Sinusitis and its Relation to General Medicine"

The Devil's Lake District Medical Society was addressed, January 28, by Dr Julius O Arnson (Fellow), Bismarck, N D, on "Clinical Recognition of the Cardiac Irregularities with Remarks on Management of Congestive Heart Failure"

Dr James B Carey (Fellow), Minneapolis, spoke before the Aberdeen District (S D) Medical Society, January 20, on "Classification and Management of the Anemias"

Dr Henry A Christian (Fellow), Boston, delivered an address on "The Clinic as a Center of Graduate Study," February 16, at a dinner given jointly by the Councils on Medical Education and Hospitals of the American Medical Association

A seminar in Physical Therapy, consisting of lectures and clinical demonstrations, is being sponsored by the New York Physical Therapy Society Dr Edgar Mayer (Fellow), Saranac Lake, opened the program, February 4, with a lecture entitled "Clinical Uses of Ultraviolet Radiation" Dr Ralph Pemberton (Fellow), Philadelphia, contributed an address on "Massage," March 4 Many other physicians have scheduled demonstrations or clinics extending as late as May 27

## OBITUARIES

## DR E. AVERY NEWTON

Doctor Newton passed away in Los Angeles on December 11, 1930. He was born in 1871 and was graduated from the University of Pennsylvania in 1902. Following his graduation Doctor Newton spent a number of years practicing at Nauheim in Germany. He came to California in 1913 and settled in Los Angeles. He very soon acquired a large following in Internal Medicine. He was a member of the County, State and American Medical Associations. He was on the staff of the California Lutheran Hospital and was made a Fellow of the American College of Physicians in 1920. He was a member of many social organizations among which were the Athletic, California and Uplifters Clubs of Los Angeles, and the Bohemian Club of San Francisco. Doctor Newton was widely known in the community in which he lived. During the last four or five years he had been incapacitated because of a heart ailment which finally caused his death.

(Furnished by Egerton Cuspin, M. D., Governor for Lower California)

## THOMAS FRANCIS REILLY

Dr. Thomas Francis Reilly was born in eastern Pennsylvania on May 30, 1871. He graduated with a brilliant record from Lafayette College in 1893, then continued to study for an additional period at Lafayette College, securing a Master's degree in Science.

He entered Bellevue Hospital Medical College, and graduated with the class of 1896. He then joined the interne staff of the City Hospital, New York City, for the period of service, 1896-1897. He was subsequently appointed Visiting Physician to the Fordham Hospital and to St. Vincent's Hospital, in both of which positions he served for a long time, and with great distinction to himself and satisfaction to the institutions. He studied abroad on several occasions, and served as Professor of Applied Therapeutics, and later as Professor of Medicine to the Fordham University School of Medicine.

He was a member of numerous medical societies, among them the American Therapeutic Society of which he was for a time president, the New York State Medical Association, the American Medical Association and many other organizations. He was a charter member of the American College of Physicians, and always attended its sessions with interest and with profit to his colleagues as well as himself. He was an extensive writer, and made many contributions to medical literature.

He was a man of fine personality, gracious manners, altruistic viewpoint and a true ornament to the profession. His passing will cause regret in the large group of his colleagues who admired and loved the man as they did the physician.

(Furnished by Harlow Brooks, Governor for Eastern New York.)

# Trauma To Viscera From Non-Penetrating External Injuries, With Special Reference To the Heart\*

By E L TUOHY, B A , M D , F A C P , AND P G BOMAN, B A , M D ,  
*Duluth, Minn*

**R**UPTURE of hollow viscus abdominal organs readily follows in man external blows, such as kicks by animals, falls from heights, or viselike compression between moving vehicles or cars. It is not so generally known that similar ruptures and tears can likewise occur to the thoracic contents. Twenty years ago such accidents occurred chiefly on farms or attended the lumber industry, today the automobile, the aeroplane, the erection of skyscrapers and general industrial activity, have expanded such injuries to an appalling extent. The great weight and high speed of automobiles, not to mention the momentum attained by falling aeroplanes, create terrific force, difficult to appreciate. A small car has been known to hit a heavy reinforced concrete bridge, shearing off its concrete side wall for several feet as if with a giant knife. The force is comparable in some degree, at least, with that of a tornado which blows straws into a tree<sup>1</sup>

An active autopsy and pathological service at St Mary's hospital, Duluth,

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\*From the Department of Medicine, The Duluth Clinic, Duluth, Minn. Read in abstract only before the Minnesota Society of Internal Medicine, Nov 11, 1929, St Paul, Minn.

and certain affiliated institutions, has yielded well over one thousand autopsies in a time period of about three preceding years. In this list there is an ever increasing number of road accidents in which chest and abdominal<sup>†</sup> injuries, with or without skull, rib, spine and extremity fractures, abound. We wish to draw upon certain of these experiences for illustrative material presented in this paper, and particularly to call attention to serious internal damage to the heart and lungs and other viscera without external bruising, consequential laceration or bony fractures.

The subject is far from a new one. The student of medical history finds that mediaeval surgery dealt much with battle injuries, as did Paré, but even without association with Mars, a rack-teering age, when every man was his own defender, invited rough tactics. Moynihan's reference to early surgery

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<sup>†</sup>Lacerations and tears have been found in almost every intra-abdominal organ except the stomach and large bowel. Incidentally, even where extensive fractures occur (including the skull) the fractures are less a lethal factor than general concussion and shock. Shock receives too little immediate attention. Too many delay in the receiving room for X-ray films of doubtful quality as well as utility.

on the protruding spleen following a butcher knife stab illustrates the point. In reference to chest injuries, Hirschfelder's<sup>1</sup> book on "Diseases of the Heart and Aorta" gives a good review, and contains useful references. Kugel<sup>2</sup> in 1909, instanced a 44 year old man who was hit by a heavy falling bale of goods. Immediate prostration and severe pain followed, with revival after stimulants, but death at the end of forty-two hours. At autopsy a rupture was found in the right auricle. One of the writers (E. L. T.), together with Dr. George Berdez<sup>3\*</sup>, in 1926 re-

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\*The original report includes the data, history and autopsy findings. Photomicrographs are shown of the area of rupture in a 63 year old man, who two weeks before death had been in an auto collision and was thrown unexpectedly and forcibly against the steering wheel of his car. The blow was sufficient to twist the wheel. Despite this and a good deal of faintness, he got about, but "felt faint frequently and vomited almost daily." He appeared to be getting better when he gasped suddenly in a deep laugh while witnessing the silent film of Harold Lloyd in "The Freshman," and was carried out of the theatre dead! No external abrasions or fractures were found. He had had a laceration near the apex into the wall of the left ventricle. Sections showed clearly fragmented muscle fibres, old hemorrhage and granulation tissue. The ventricle ruptured through at this point. He had atherosclerotic arterio-sclerosis, with some of the coronary arteries patent in their main branches.

ported "two instances of perforation of the heart following non-penetrating chest injury." These illustrated the contrast between early death from ventricular rupture, and delayed death after a beginning repair in a heart wall laceration. There is much more in the literature on immediately fatal cases of rupture than on functional perversions appearing after such injuries. Much interest centers about a report on the subject by the Kahns (Maurice H. and Samuel)<sup>4</sup> published in April, 1929. Their article has particularly great industrial interest. While there is no autopsy confirmation of some twelve cases presented, the clinical data are clearly given, and there are some fifty-five literature references. The authors discuss the results on cardiac function (notably rhythm and conduction alterations) after direct and indirect chest injuries inducing "contusion and concussion," concluding rightfully that on these matters the present literature is quite meagre.

We may proceed, therefore, with the knowledge and the certainty that just as the abdominal organs† suffer tears

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physiologists that even with heart rupture the organ carries on until the pressure outside of the chambers in the pericardial sac equals that within, when contractions cease. This likely is the reason for the need of early surgery in suspected chamber leakage after injury, and the explanation of increas-

and contusions so also the same type of trauma may damage the contents of the thorax. Since not all of these result fatally at once, or death is postponed some time, it seems fair enough to enter into a cautious discussion as to the possible functional disturbances, particularly of the heart, that may result after injury, and in these non-fatal cases it is possible that we may find an explanation of certain aftermaths of injuries that we erroneously label cardiac or compensation neuroses.

As to the mechanism of hollow viscus damage after injury, all writers agree with Hirschfelder<sup>1</sup> upon the influence of unchecked and unexpected force expended at a time when a contracting muscled organ, full or partly full of near liquid contents, is suddenly compressed. There is in the literature much repetition of such accidents as falls from heights to hard surfaces or to water, planks or cases being pulled or tipped upon the worker, cars slipping off supports and jacks, settling upon the victim with great force, truck handles or squeezing injuries between rigid walls or moving cars—all providing infinite variety.\*

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mobile accident, where death resulted from severe skull fracture and brain concussion. Despite the fact that he had no abrasions over his liver area (and indeed, the liver capsule itself was unbroken) there was a large area in the middle of the right liver lobe extensively crushed and lacerated, with resultant hemorrhage. It is well to recall that this type of liver injury, where the patient survives, is often followed by extreme hyperpyrexia.

\*Our autopsy service has produced two instances of rupture of the aorta itself, but they are not included in this report because almost no clinical data were preserved with the records.

The Kahns'<sup>1</sup> article introduces certain criteria bearing upon the question of relation of disability and injury to compensability. While this matter of compensability need not have intimate relationship to demonstrable pathological sequences, and is more a legal than a medical assignment, yet much of our vaunted "science of medicine" is based on empirical experiences no better founded than subjective disability and incapacity from usual work. Naturally this kind of evidence is materially strengthened when objective data, such as arrhythmias, changes in heart outline or in electrocardiograms, are available. In effect, these are the Kahns' statements:

1 From the standpoint of labor and compensation a man is healthy if he has been able to work for a long period without distress or long interruption.

2 If such a man has a direct or indirect violence applied to the chest and develops incapacitating cardiovascular states, these must be considered to have arisen from an aggravation of a previously existing asymptomatic condition or arisen from damage to a previously normal heart.

3 There must be prompt development of symptoms. "Pain, with its concomitant dyspnea, rapid, irregular pulse, faintness, prostration, cold sweats, etc., in order that casual or aggravating relationship be clearly established." Recurrence of symptoms after temporary improvement is said to be attributable to the original injury. (While such dicta are a good basis of discussion, they cannot be taken as final criteria. For example, most of the sudden signs mentioned under paragraph 3 can arise from basal brain in-



juries, without especial chest localization )

Localizing evidence in terms of heart outline and contours, demonstrable perversions of rhythm and conduction, decisive evidence of heart incompetency, lend increasing certainty in living clinical cases, the victims of chest injury. There still remain two fields in which our impressions and surmises in terms of their trauma offer interesting speculation. We refer to the group with previous cardiovascular disease (chiefly sclerotic changes yielding the background for rhythm and conduction disturbances), and the functional group that must closely border upon traumatic neuroses. We may state that neuroses, while occurring at all ages, are more characteristic of the young, and arteriosclerotic phenomena of the ageing. Therefore, an instance of auricular fibrillation, occurring in a truck driver aged 20 (reported by Levison<sup>2</sup>), has unusual bearing on this subject. This young man, after a severe crushing injury of his thoracic region, developed severe pain over the precordium, accompanied by violent dyspnea, but without cyanosis. There was a marked pulse deficit (the rate was something about 150). No electrocardiogram was taken until some thirty-six hours later, when normal rhythm had been restored. Levison discusses the question of liability and the relation of auricular fibrillation to an individual's capacity. Bearing upon the question of the previous status of the heart, he observed that most individuals while they may not be conscious of a recently developed auricular fibrillation, still are questioning that their

capacity has been suddenly and decidedly reduced.

The Kahns<sup>4</sup> also report the instance of a well nourished man of 33, who was hit by a heavy plank falling on his chest from a height of about eighteen feet. "During two weeks of hospital observation he felt weak, with pressing pain across the front of the chest." Some three months later his heart was not enlarged, but an electrocardiogram showed coarse auricular fibrillation with tachycardia. Quinidine sulphate promptly restored normal rhythm. They stated that no such condition as rheumatism, syphilis or arteriosclerosis, Graves' disease or toxic agents, could be shown to have any connection with his illness, and the size of the heart precluded previous valvular or pericardial disease or a hypertensive background.

One of us (E. L. T.) saw in consultation a 36 year old man in January, 1926, who had an obvious auricular fibrillation.<sup>\*</sup> Two days previously he had been hit on the chest by the heavy limb of a falling tree. Because of an associated nervousness, coarse tremor, and some slight enlargement of his thyroid he was studied from the standpoint of a possible instance of hyperthyroidism, influenced by the shock of his injury. He had no weight loss, there was no unusual feeling of bodily warmth and several basal metabolic readings were within normal limits. We ruled (possibly erroneously) that his injury had no connection with his heart situation, and the man passed out from under observation.

<sup>\*</sup>Paroxysmal auricular fibrillation must always be considered in these traumatic problems.

The question is immediately presented, if we do attribute these instances of auricular fibrillation to injury as to where the damage occurs to the heart and what is its general nature. Are we dealing with laceration, hemorrhage, edema, or lesser grades of concussion, such as are better understood in terms of damage to the cranial contents? This question, particularly related to hemorrhage assumes an even greater position of importance in terms of heart block in conduction disturbances.

C. Thiem<sup>6</sup> in his handbook of diseases due to accidents instances the case of a beer deliverer who was kicked in the left chest by a horse. He retained for fourteen days a feeling of substernal oppression, with a sense of impending death, and had some pain distribution down the left arm. Fifteen months later he died in an anginal seizure. The interventricular septum showed definite evidences of old hemorrhages, with resulting scar. It was concluded by the reporters of the case that there had been a hemorrhage induced into the interventricular septum, leading to a conduction disturbance. Unfortunately, no clinical data accompany the report which would help to determine the type.

We have closely studied a male 70 years old, who for many years carried on efficiently as an employee of a department store. Some of his duties involved the carrying of heavy sacks of material weighing as much as one hundred pounds. These he usually lifted to his shoulder and he managed to do so without undue fatigue, dyspnea or distress. On Aug 6, 1928, he tripped and fell on a stairway in such a manner as to hit his thorax a stun-

ning blow. There was immediate pain, rather generally through the chest, chiefly about the left side. While he was stunned he was not unconscious. Breathing deeply did not greatly increase his pain. There was an impression after bringing him to the hospital that there might have been a cracked rib, but no fractures nor displacements were found. He remained in the hospital only three days, but on returning home he continued to have persistent discomfort over the precordium, and had to get about quite cautiously. On his return to the hospital Sept 10, 1928, an electrocardiographic study (Fig 1) made by one of us (P G B) showed a complete heart block. Five weeks later, on re-examination, he had normal sinus rhythm, but right bundle branch block (Fig 2)—this condition lasting for about ten or twelve days, when the complete block returned, together with the evidence of the right bundle branch block—and this has remained up to date (Fig 3).

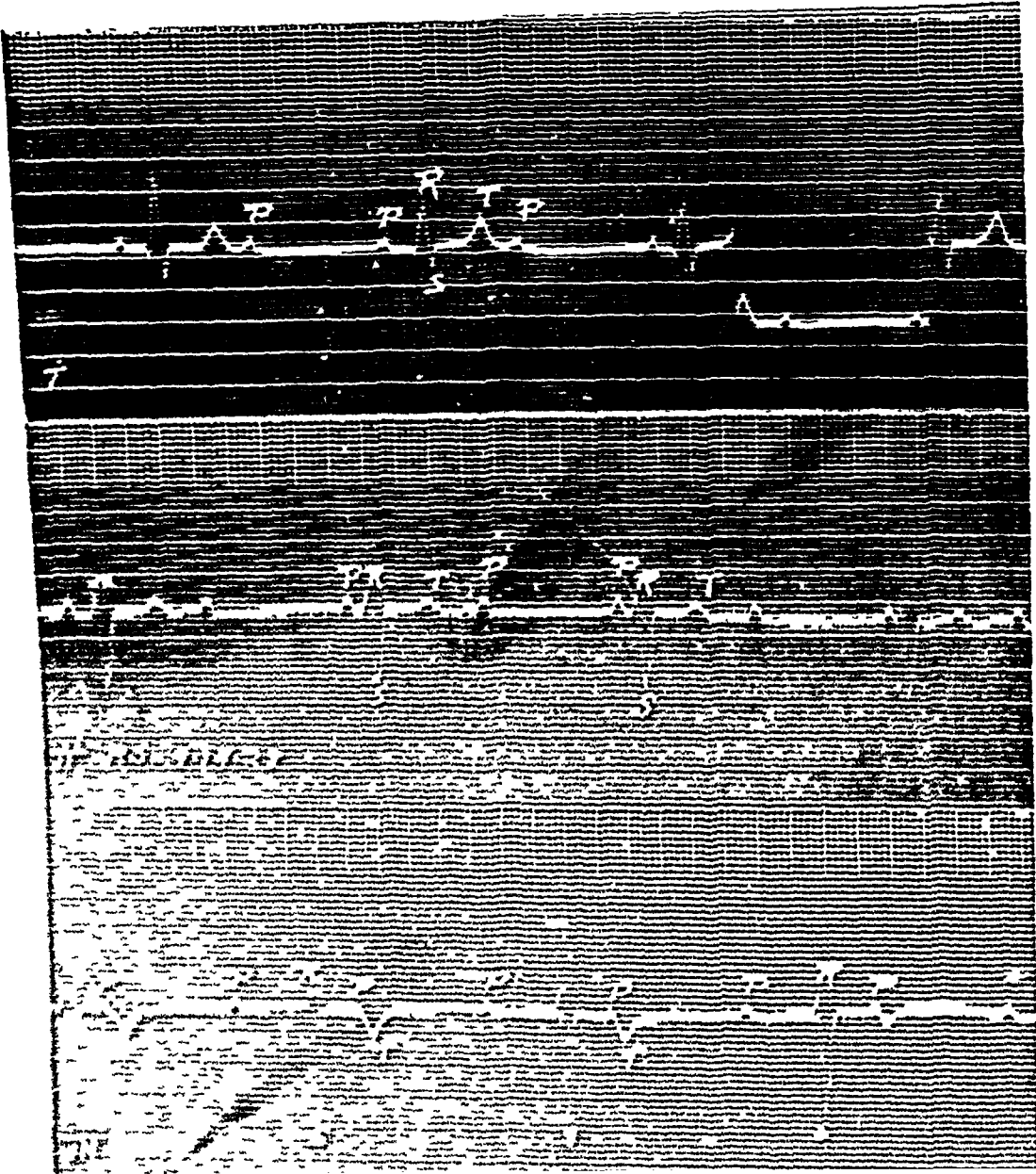
This 70 year old man has plenty of evidence of generalized arteriosclerosis. What was the relationship of his injury to this decisive interference in his conducting mechanism? The answer could be more dogmatically given could the interventricular septum be carefully examined grossly and microscopically within the few weeks after the onset of his block. Fortunately, however, he has continued to live, and we are forced to enter upon a certain degree of speculation.

Two general hypotheses present themselves. This 70 year old man came by his conduction disturbance through the usual route of myocardial fibrosis, with localization in the interventricular

septum and affecting the bundle of His, independent of his injury, or, the injury induced traumatic sequences, the most likely of which is hemorrhage into the same area. Premortem hemorrhage into this area of the bundle of His is not uncommonly divulged at

postmortem. We recall the instance of a man dying from brain tumor who showed such a hemorrhage that must have precipitated his death.

Lubarsch<sup>7</sup> discusses this important issue of hemorrhage into the heart muscle in various regions, commenting



upon the well known local and constitutional active and predisposing states. Naturally, the signs and symptoms must vary greatly, dependent upon the site where exudation occurs the junctional tissues yielding a maximum of conduction disturbances even with

very limited areas involved, rhythm and rate disturbances following readily upon invasion of areas about the sinus and sino-auricular node

Particular interest centers about the interventricular septum in terms of the greatly increasing knowledge and lit-

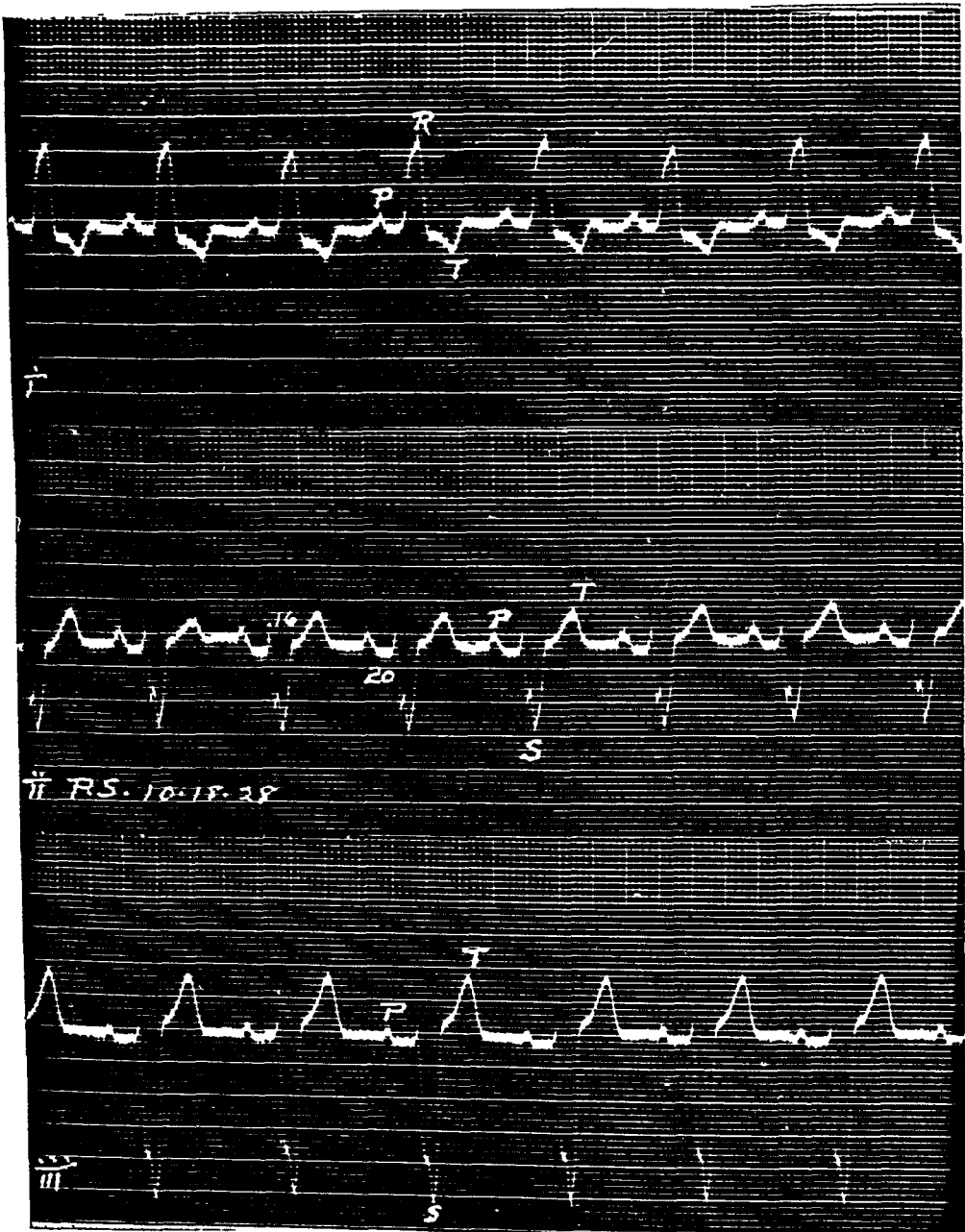
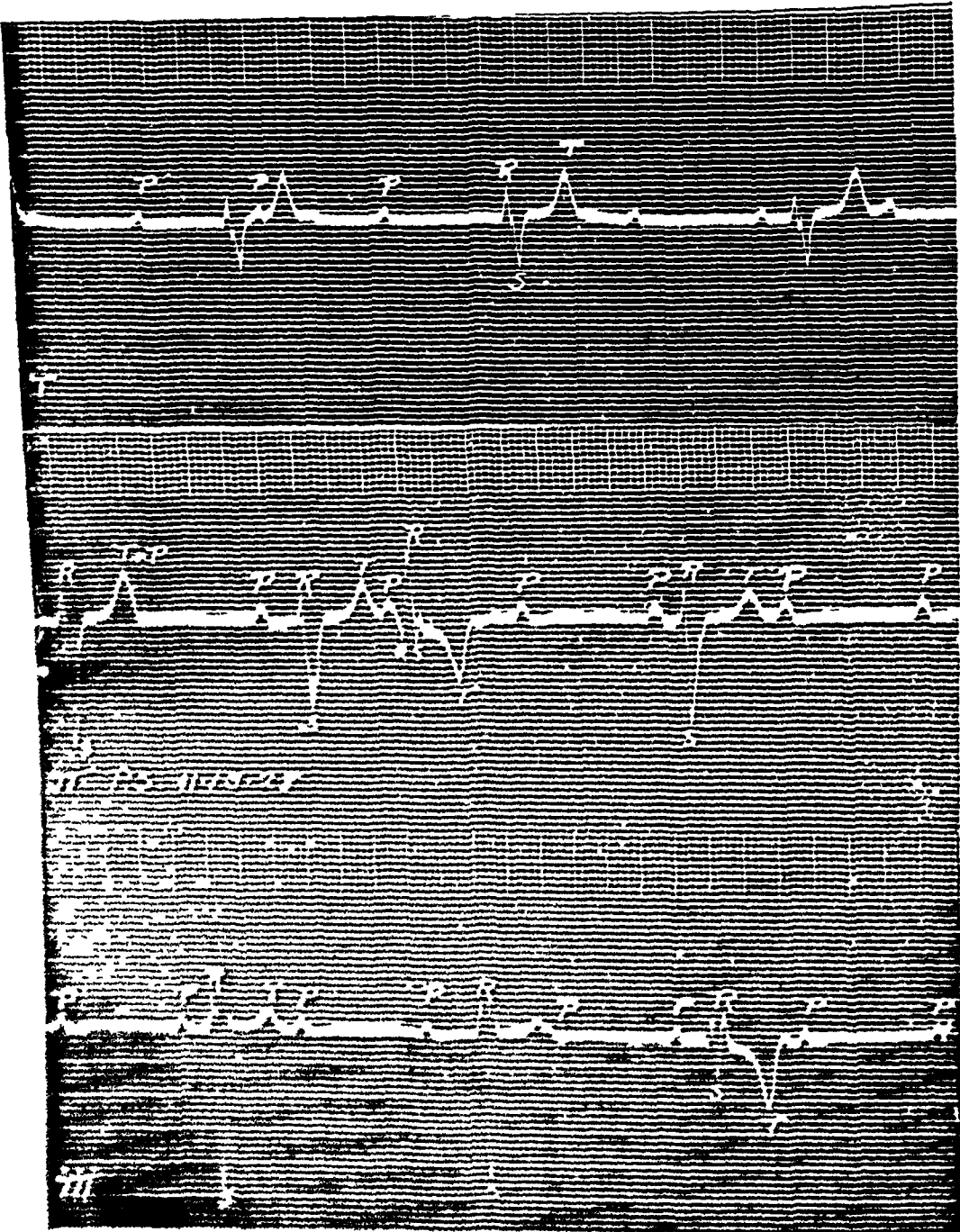


FIG 2 Record shows a normal sinus rhythm, with an auricular and ventricular rate of 70. A complete right bundle branch block is present.

erature on the coronary blood supply to the heart and its normal variations Whitten's<sup>8</sup> injection and corrosion methods in studying heart vasculature, have conspicuously helped in identifying the normal, with its variations, as

well as the abnormal and its anastomotic possibilities The application of this knowledge has been found in the sequences known to follow infarction in the main division of the coronaries T wave studies by many English and



American authors<sup>9 10 11 12 13 and 14</sup>, with especial references to the variations in the ventricular complexes in established cases of myocardial infarction and fibrosis, while not yet yielding us unvarying characteristic forms, still have greatly expanded cardiac lesion localization to something comparable with brain localization in terms of motor and sensory phenomena. While it cannot be stated without reservation that the absence of characteristic ventricular complex changes in our patient rules out infarction, still the evidence is strongly corroborative that it did not exist. As a matter of fact, the clinical evidence admits of finer differentiation even than does the pathological. The distinction between infarction and hemorrhage into tissues is one of degree, because the events of infarction leading up to anemic necrosis or connective tissue replacement include early hemorrhagic infiltration into the infarcted area. We may simply state that the electrocardiographic evidence in our man gives no hint as to infarction. He has had no evidence of syphilis, and only moderate hypertension. Something happened to him to give him his total heart block, but it was not fully established until sometime after our observation began. The evidence is clear that a shifting status as to degree and type supervened: a total heart block, followed by a period of branch bundle block, to be later followed by a combination of both. We consider this of some importance as indicating that his complete block was not the result of a fixed pathological lesion, but gradually became so. Hemorrhage could explain this sequence, even as it did in C. Thomsen's report of the case

of the man kicked in the chest by a horse.

In fortunate contrast to this instance of an elderly man we have full data upon an apparently otherwise healthy man, aged 43, as follows:

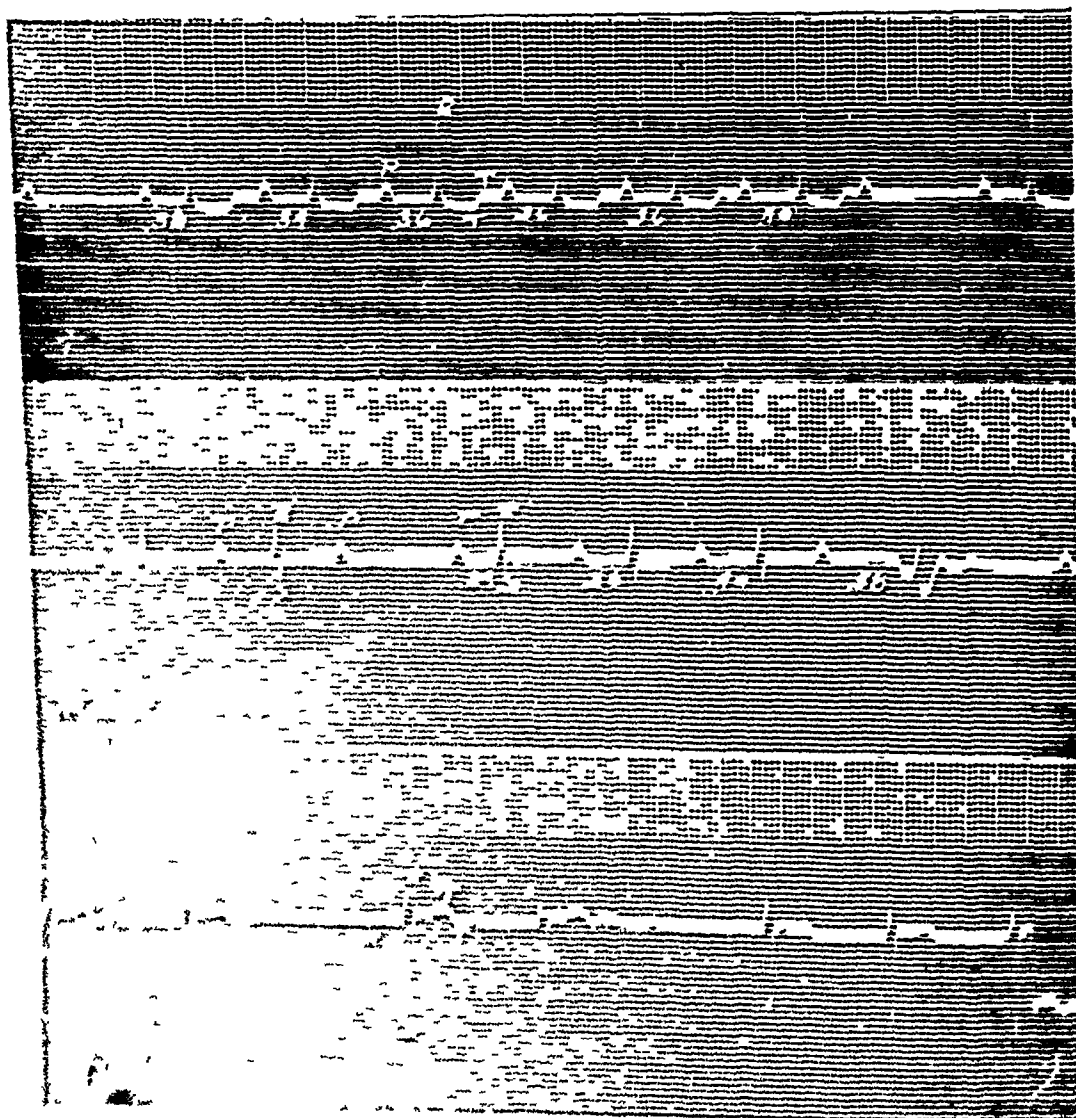
Mr. D. A., while in a stooped position lifting a very heavy manhole cover in the street, felt immediately faint, soon he "began to sweat profusely and there was a pain across the chest, down into the left arm." This only lasted a few minutes. He pulled himself together and finished out his afternoon's work, but felt very poorly. The following morning, after breakfasting and attempting to leave his house, he stopped on the sidewalk with a great sense of weakness, dizziness and a feeling of impending disaster. He remembers that there was soon a feeling as of impending movement of his bowels, and then he fainted. Fifteen minutes later a physician saw him, and stated that "his pulse was very slow (down to about 26)." That day and the next the pulse gradually came up to 50 and 60, but he continued to be extremely dyspneic, and found it almost impossible to lie down or sleep.

When brought to us a week after his strain he appeared very ill: pallid, slightly cyanosed, rapid shallow breathing, and an anxious appearance. Taking his pulse at the wrist there were occasional dropped beats, but the others seemed fairly evenly spaced. The neck veins were markedly overfilled, the liver edge pushed down and felt rounded, there were many non-resonant râles at the bases of the lungs. The heart outline was extended moderately to the left. Three tones were distinctly heard at the apex (splitting of the first tone?), and there was a short, puffing systolic murmur. Branch bundle block was suspected. The electrocardiogram (Fig. 4), however, showed instead the increasing P-R conduction interval known as the "Wenckebach period." This most interesting set of electrocardiograms is reported at this time, not to emphasize or elaborate upon this rare and unusual electrocardiographic evidence of an odd type of block, but to further introduce evidence as to the possible relationship between strains

f a severe type and heart conduction interference. His disability continued, but gradually cleared up. (See electrocardiographic tracings, with their explanation—Fig 5.)

One month after his strain and the development of his difficulty he had apparently returned to normal in terms of his feelings, capacity, and heart tones, with a complete disappearance of his dyspnea and signs of passive congestion. The electrocardiogram was then practically normal, with the exception of evidence of slight left ventricular preponderance (Fig 6).

This sequence is in itself interesting, since certain positive findings can be submitted to support the assumption that a sudden lift was followed by incapacity and an objective insult to the heart. His story is further complicated by his statement that seven years previously, after a severe strain in fitting a heavy plumbing connection, he had almost the same type of pain, dyspnea and disability, but of lesser severity and lasting in all about one week.



He offers no neurotic tendencies, and is all too eager to get back to work, he is extremely definite in his statement as to the parallelism which existed between the two spells

To attempt to identify his pathology is admittedly difficult. Because of his dramatic improvement and the site of the heart block, coronary infarction can be ruled out. As to the auricular fibril-

lation cases no one speaks with much certainty about the circulatory channels in the auricles. Indeed, aside from the epoch making discoveries of Keith and Flack and those of Tawara, little is known about the neuromuscular auricular tracts.

The thesis we have been developing leads up gradually from severe lethal trauma to the heart, through disturb-

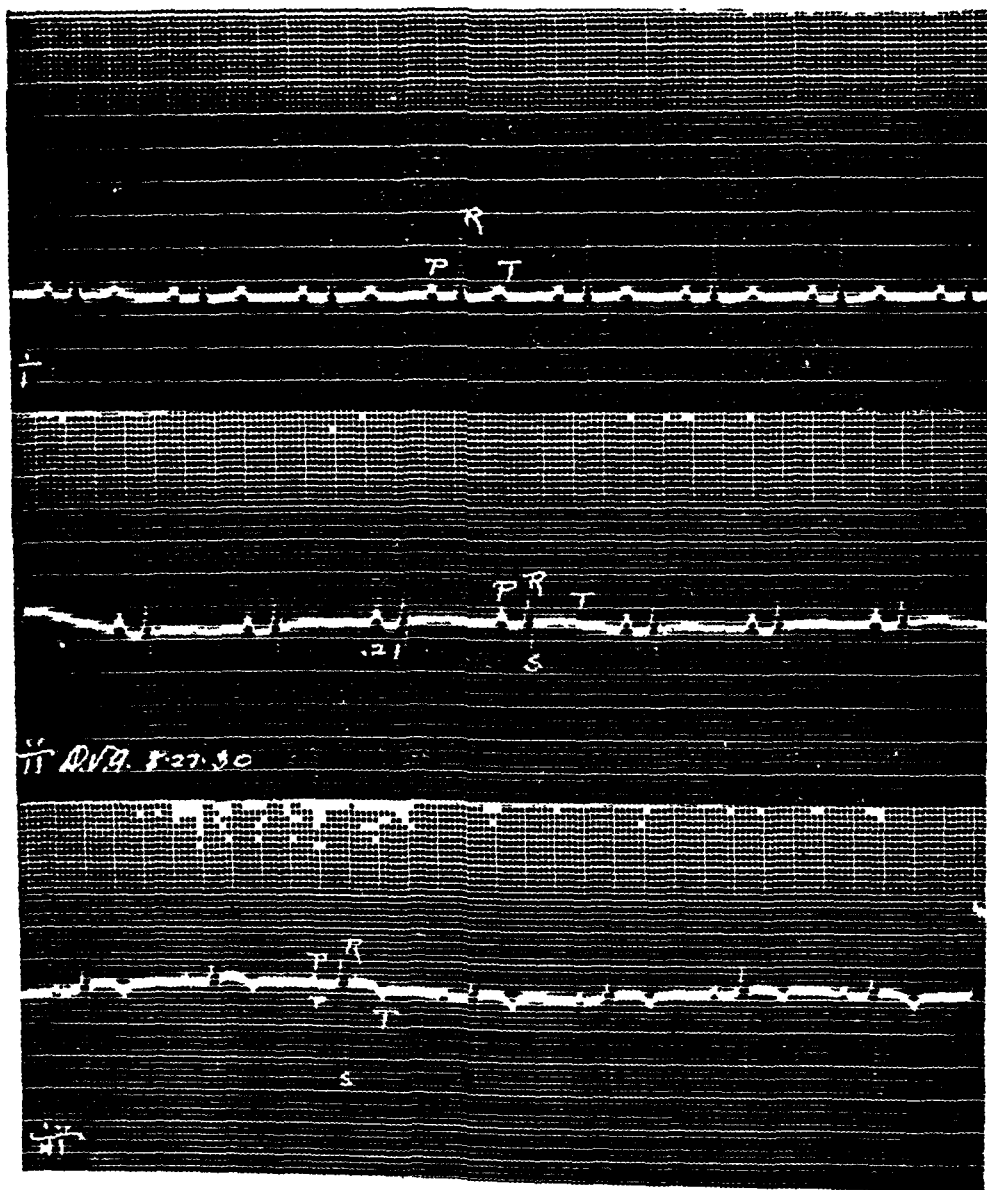
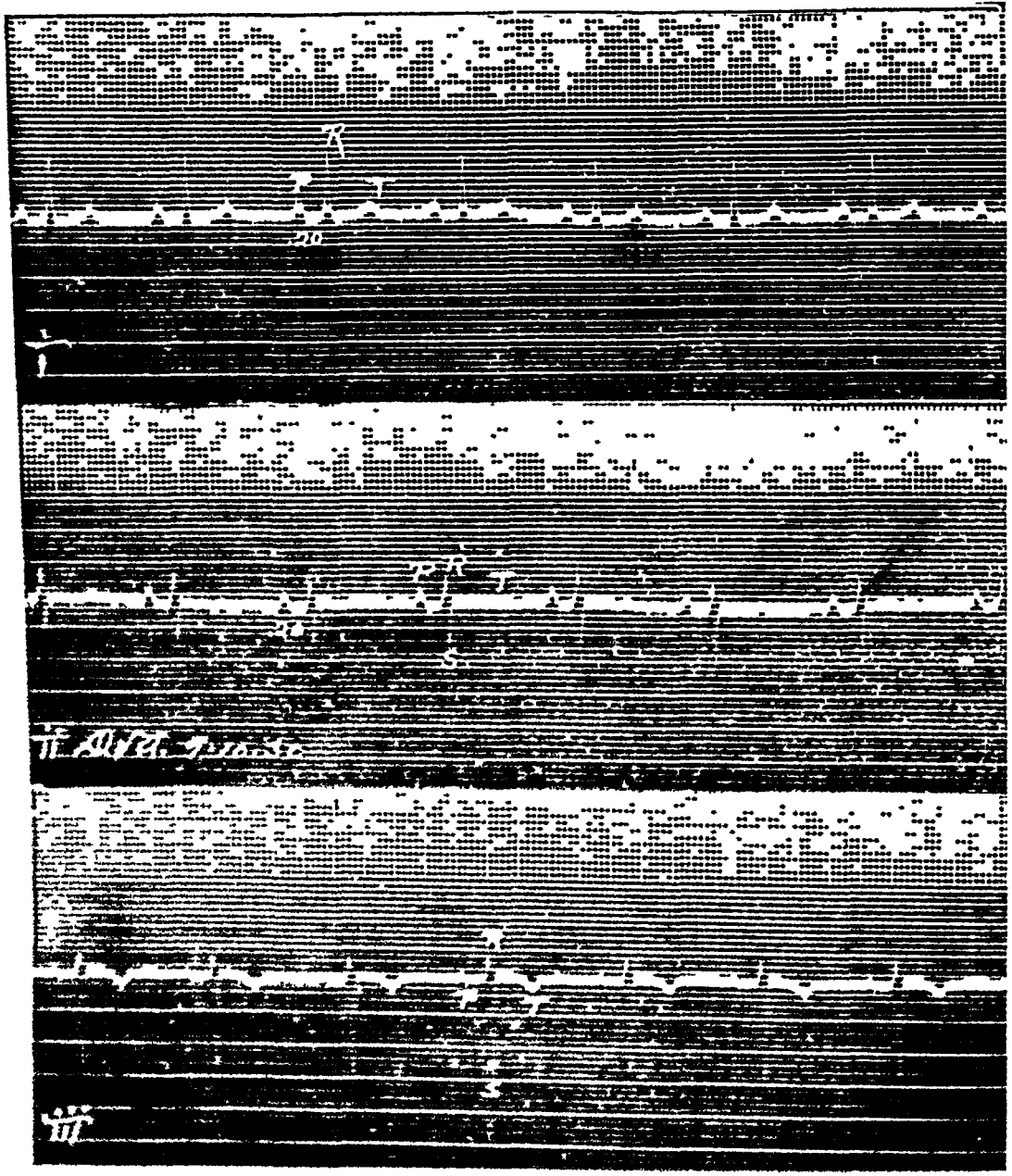


FIG 5 This record shows a definite improvement in the conduction of the auriculoventricular node, and contains a uniform P R interval of 0.21 of a second. An improvement is also noted in the T wave.



ances of function that permit of objective demonstration, to a final word on cardiac instability and subjective incapacity following upon localized chest trauma We guardedly enter upon a discussion of this group for reasons fully obvious to all those who see many instances of so-called cardiac neuroses or poorly employed by-products of a mass production era In retrospect, it

occurs to us that in the past we may have paid too little attention to persistent heart symptoms—arrhythmia, actual or near approach to paroxysmal tachycardia—following chest injury It is well to remember the devastations known to follow cerebral concussion—even without fracture of the skull—where severe shock and memory effacement have obtained



A vigorous young woodsman, Mr F. W., aged 19, from the upper Michigan lumber woods came for examination in August, 1929. About one year previously he had suffered from "a severe strain of his chest when pulling upon some heavy ties," which was his regular sawmill work. These ties were rather heavy, and as they came from the saw it was his job to grasp them and drag them toward himself with a pair of tongs. After a pull in which he partially lost his balance he stated that "something seemed to let go in my chest and throat."

Here we were dealing with a young phlegmatic boy, who had never been conscious of his chest before nor had he lost any time from work. His chest was strapped up, and he complained of more or less discomfort for about three weeks. At recurring intervals for the intervening year he tried to go back to this work, but after a day or two would again experience the same severe, lancinating pains in his chest, and had to give it up. He described these pains as a feeling of tearing within, followed soon thereafter by a sense of suffocation, that greatly annoyed him but did not seem to be accompanied by an appreciable tachycardia.

Our examination involved everything of an objective nature commonly done. Particular evidence was given to the possibility of the various types of diaphragmatic herniation. Nothing whatever objective was found.

An insinuation comes to mind also of a somewhat older man (35 years), seen first in September, 1929. One year previously he had been the victim of a cave-in in an underground iron mine. He remained thus engulfed for nearly two days, and when removed was naturally very exhausted. Thereafter he gradually recovered, but very little effort continued to bring on distress in his chest, with a tendency to palpitation. At examination objective findings were again total-

ly lacking, including electrocardiographic tracings, outlines of the heart, esophageal and gastric barium visualization, etc. He had sweaty hands and the makeup suggesting the indefinite syndrome of "irritable heart." He was markedly improved under a systematic plan of deep breathing, re-education and graduated exercise.

The lung can also show violent tears from non-penetrating and non-fracturing chest blows. A 12 year old boy after a car accident had a 4 inch laceration deeply into the lower right lobe of his lung, and died of general shock as well as hemothorax. At autopsy his ribs and sternum could be easily pressed down and flattened out against the spinal column without any rib fracture, with full restitution to normal external relation on release. Two boys rode at very high speed into an express train in a fog at a crossing. The one was decapitated, the other (aet 20) had many body and chest contusions, a fractured right clavicle and multiple left leg fractures. Just as he developed a choking of his optic discs without skull fracture, he developed after extreme shock a shift of his heart markedly to the right, with a drop of his diastolic pressure to zero, with extreme cyanosis, all without rib fracture. The oxygen tent rescued him both from his shock and massive atelectasis accompanying internal pulmonary hemorrhage. For four days he spit up considerable blood, but ultimately recovered.

#### COMMENT

The subject which we have discussed is a sort of "no man's land" between medicine and surgery. Increasing interest is manifested as indicated in a slowly developing literature. Internists should take an interest in it, sur-

over to safety and some years of comfort

## CONCLUSIONS

I Youthful resilient thoraces permit extreme compression without fracture

2 The thoracic viscera, like the abdominal, may be torn and lacerated—early and late heart chamber rupture may result, all without even external bruising

3 Granting this, it must be possible that non-fatal degrees of laceration and hemorrhage may occur. These, with edema or simple trauma, may induce definite physiological perversions. Auricular fibrillation and degrees of heart block are discussed.

4 The border ground between traumatic or compensation neuroses and actual cardiac distress after chest injury is touched upon

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# Chronic Meningococcemia Without Localizing Signs\*

## Report of a Case

By SAMUEL S RIVEN, M D, *Nashville, Tenn*, AND ABEL A APPLEBAUM, M D, *Ann Arbor, Mich.*

CHRONIC meningococcemia without localizing signs is a comparatively rare disease, although more frequent reports of its occurrence have appeared in recent years. It offers an explanation for a limited number of cases of prolonged fever without any apparent cause. Gwynn in 1898 first demonstrated the meningococcus in the blood stream. Salomon<sup>1</sup> (1902) described a sepsis which persisted for eight weeks and repeated positive blood cultures for the meningococcus were obtained. A localization of the sepsis in the meninges was noted later. Further instances of meningococcus septicemia have been reported by Andrewes<sup>2</sup>, Liebermeister<sup>3</sup>, Warfield and Walker<sup>4</sup>, Morgan<sup>5</sup>, Neergard<sup>6</sup>, Graves, Dulaney and Michelson<sup>7</sup>, Spirit and Braun<sup>8</sup>, Lemmers-Danforth<sup>9</sup>, Dock<sup>14</sup>, and Vesell and Barsky<sup>10</sup>. In all cases diagnosis was made by bacteriological procedures or necropsy.

The source of infection by the meningococcus has been in dispute for some time. Without a doubt the or-

ganisms are first harbored in a focus most commonly located in the nasopharynx. It was thought at first that infection of the meninges took place by direct extension from the nasal mucosa through the ethmoidal cells and cribriform plate of the ethmoid. The infection may spread through lymph channels or more likely the blood vessels (Herrick<sup>11</sup>, Elser and Huntington<sup>12</sup>). Herrick emphasizes that a meningococcemia always precedes involvement of the meninges and is characterized by symptoms of sepsis lasting several hours to several days during which time the organisms may be isolated from the blood stream. The majority of reported cases including the one under discussion here present evidence for the hematogenous route of infection.

Various classifications of meningococcemias have been presented, of these probably the most complete and more recent is that of Graves, Dulaney, and Michelson<sup>7</sup>. They divide meningococcemias into two main groups, the acute and chronic. Acute meningococcemia is that form in which general sepsis is of less than one week's duration prior to localization in some one

\*From the Department of Internal Medicine, University of Michigan Hospital, Ann Arbor, Michigan

organ. This includes the fulminating type with a fatal outcome in from eight to twenty-four hours after the onset, and also the type which is followed by localization in the meninges. Chronic meningococcemia is the form in which the sepsis is present more than one week and terminates in most cases by localization (meningitis, endocarditis) or, in a few instances, by a continuation of the generalized form of the disease.

To date, seventeen cases of chronic meningococcemia have been reported in American medical literature, although a much larger series appears in foreign periodicals. Of these seventeen cases including the one reported here—five showed localization in the meninges with recovery, one had localization in the endocardium and then metastasis to the meninges and death, two localized in the endocardium and terminated fatally. A second group of nine showed no localization, of these eight recovered. The case reported here falls into this infrequent form of chronic meningococcemia without any localization or metastasis.

redness, swelling or heat over the joints. These symptoms were not continuous but would come about once a week associated with fever and mild sweats and would last for two or three days. About June 1, 1930, a little over one week after the onset of his illness, the patient noticed a rash appearing first on the dorsum of his left foot and then in varying degrees on the arms, legs, palms, soles and trunk but none on the face. These lesions, he described as varying in size from pin-head to pea size, were rose colored, elevated, not painful, and underwent involution in the course of one week leaving a brownish hyperpigmentation. The skin lesions appeared in crops accompanying the rise in temperature and generalized symptoms described above. During his illness the patient was constipated, appetite was poor, and he lost about fifteen pounds in body weight in seven weeks prior to admission.

The past history threw no light on the present condition. There were no other people in his community suffering from a similar illness.

*Physical Examination*—The patient was a middle-aged foreign male who appeared fairly well nourished, but ill. There was no apparent pain or discomfort. The skin and mucous membranes showed a distinct pallor. On the extremities and trunk there was a maculo-papular eruption with the lesions undergoing various changes of involution, the color ranging from rose to brownish pigmentation, size varying from pin-head to pea size, deeply seated and only slightly elevated above the surrounding skin. They were fairly firm to palpation, and not tender. The lymph glands, including the cervical, axillary, epitrochlear, and inguinal glands were moderately enlarged, discrete, but not tender. The pupils were equal and reacted to light and accommodation. The fundus examination revealed no abnormalities. The teeth showed caries and there was a definite pyorrhea present. The throat was not reddened and there was no exudate. There was no tenderness over the sinuses, antra or mastoids. There was no stiffness of the neck. Examination of the heart and lungs was negative except for a few crackles at the right apex which disappeared in the course of a few days. Blood pressure was

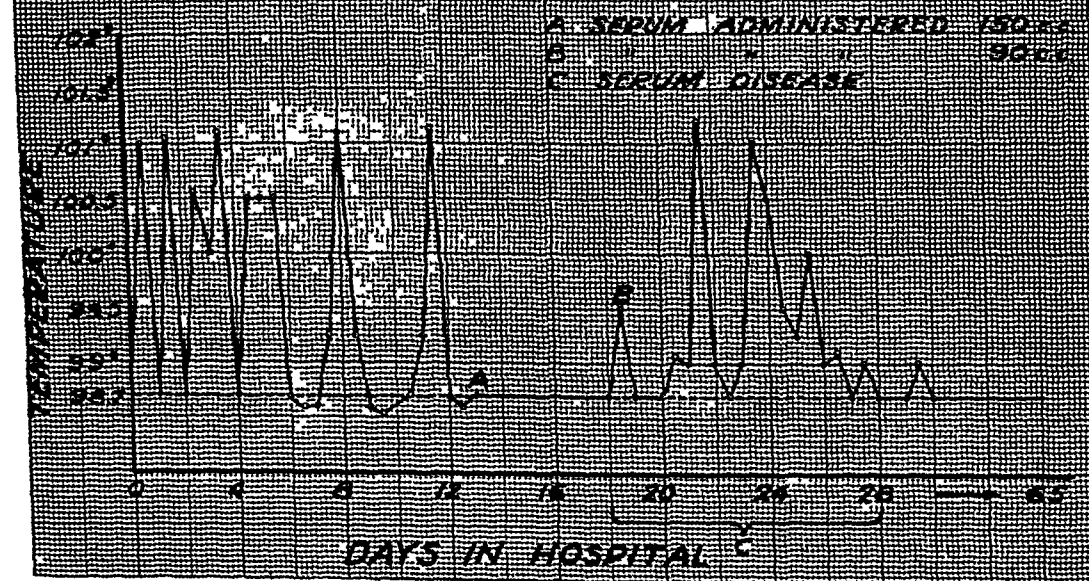
128/75 The edge of the spleen was just palpable, further examination of the abdomen showed no gross abnormalities. The joints were freely movable both on active and passive motion. Neurologic examination revealed no neck rigidity. The pupils were normal. There was slight weakness of the left side of the face. The biceps, triceps, knee, and Achilles' jerks, and abdominal reflexes were increased in intensity. No Kernig sign, Brudzinski sign, Babinski sign or ankle clonus was present. Considerable tremor on finger to nose test, more on the right side, was present with the eyes both open and closed. There was no evidence of meningeal irritation except the increased intensity of the reflexes which may have been present prior to the patient's present illness, these findings were more compatible with a mild toxemia than any other form of central nervous system involvement.

The tentative diagnoses on admission were undulant fever, typhoid and paratyphoid fever, secondary stage of syphilis with roseola, erythema nodosum and pulmonary tuberculosis.

#### Course and Treatment —

The Kahn test of the blood serum for syphilis was negative. Blood culture and agglutination tests for *B. melitensis*, *B. tularensis*, *B. abortus*, *B. typhosus* and paratyphosus taken on August 7, 1930, were reported negative and the blood culture showed no growth on the third day. There was a slight anemia present—hemoglobin 76%, (Sahli), red blood cells, 3,700,000 per cu mm, white blood cells 14,800 per cu mm. X-ray examination of the chest was negative, showing no evidence of pulmonary tuberculosis. The temperature was intermittent in character with an afternoon rise to 101° F and fall to normal during the night and morning (see table No 1). From July 9 to July 11, 1930, the temperature remained elevated to 100.3° F and associated with this rise there were pains in the arms, legs and occiput, and a feeling of malaise. With this myalgia and arthralgia a maculopapular rash appeared. On July 11, 1930, the temperature fell to normal and the pains and rash disappeared. On July 13 and again on July 16 there was a morning febrile rise

TABLE No. 1



to 101.4° with the same symptoms noted above. During these rises the white blood cell count rose to 20,000 per cu mm. Blood cultures were taken at the height of the fever. After seven days cultivation of the first blood culture and two days cultivation of the second, both flasks showed a growth of gram-negative diplococci which were agglutinated by polyvalent anti-meningococcus serum.

On the basis of the laboratory findings a diagnosis of meningococcemia without any localization was made. No lumbar puncture was done because of the absence of symptoms of meningeal irritation and the possibility that it might favor localization in the meninges.

On July 18th after routine desensitizing doses of horse serum he was given 60 cc of polyvalent antimeningococcus serum intravenously. On the following day he received 90 cc more making a total of 150 cc of serum. There was no immediate reaction from the serum except for a slight backache which passed off at once. Smears were taken from the nasopharynx which were reported as positive for the meningococcus. Following the first serum administration the temperature promptly dropped to normal for 5 days and all symptoms subsided. On July 23rd there was a slight febrile rise to 99.4° F, recurrence of symptoms was feared and the patient was given 90 cc of serum intravenously in 3 doses of 30 cc each. On the seventh day after administration of the first serum the patient developed serum sickness which subsided after treatment with epinephrin and ephedrin. Repeated consecutive

blood cultures taken at intervals varying from four days to two weeks were consistently reported as showing no meningococci (See table No 2).

On July 18th swabs were taken from the nasopharynx. Direct smear and culture both showed the presence of meningococci. Saline irrigations of the nose and throat followed by instillations of 25% solution of argyrol were instituted three times a day. Nasal cultures remained positive even in the presence of negative blood cultures until August 17th after which time repeated nasal cultures were negative. After the temperature had subsided the patient was placed on a high caloric diet and in the course of six weeks gained twenty-four pounds in body weight. His general condition improved remarkably and he was discharged as cured on September 7, 1930, one hundred twelve days after the onset of his illness or sixty-five days after admission to the University Hospital.

#### ADDITIONAL LABORATORY DATA\*

The first two blood cultures taken on July 7th and July 16th were positive for the meningococcus. Six succeeding cultures at varying intervals after the administration of polyvalent antimeningococcus serum showed no growth. For five weeks prior to dis-

\*Laboratory work in this case was carried out in the University Hospital Bacteriological Laboratories under the direction of Doctor R. L. Kahn and Miss L. D. Henry.

TABLE No 2

BLOOD CULTURES		CULTURES OF NASO-PHARYNX	
Date	Result	Date	Result
7- 7-30	meningococci	7-18-30	meningococci
7-16-30	"	8- 1-30	no meningococci
7-18-30	antimeningococcus serum given	8- 9-30	meningococci
7-18-30	no growth	8-11-30	meningococci
7-23-30	no growth	8-13-30	no meningococci
7-28-30	no growth	8-16-30	no meningococci
7-28-30	no growth	8-19-30	no meningococci
8- 1-30	no growth	8-23-30	no meningococci
8- 7-30	no growth	9- 2-30	no meningococci
8-23-30	no growth		

charge he had a negative blood culture. Beef infusion, glucose broth, liver-brain infusion or Hibbler's broth, beef infusion agar and Hibbler's agar poured plates were employed. All media prior to sterilization were titrated to pH of 7.5. The sediment in the flasks of broth and the colonies on the agar plates were examined daily, stained by Gram's method and the type of organism and number of colonies noted. As soon as growth appeared in the sediment a transfer was made to blood agar plates, and from the growth here a bacterial antigen was made and this was agglutinated against the routine diagnostic antisera as well as all obtainable lots of therapeutic antimeningococcus serum. Controls were run in each instance. A correlation of the cultural, morphological, and serological characteristics of the organism found showed it to be a Gram-negative diplococcus which was agglutinated by all available antimeningococcus sera in dilution of 1:320.

Nasal cultures were positive for the meningococcus from July 18 until August 13 after which time they were negative on five consecutive occasions prior to discharge on September 7, 1930.

#### COMMENT

In view of the increase in the number of reported cases of chronic meningococcemia in recent years, an analysis of the findings seems timely. This is an analysis of the seventeen cases of this disease reported in American medical literature to date.

*Duration*—The average length of illness was four months, the extremes being from three weeks (Cecil and

Soper<sup>13</sup>, Herrick<sup>21</sup>) and seven months (Dock<sup>14</sup>).

*Age*—A sepsis of this type may occur at any age period. The youngest patient in this group was twelve years (Marlowe<sup>15</sup>) and the oldest forty-four years. Ninety-two per cent of the cases fell into the third and fourth decades of life. The disease apparently is more predominant in males than females (3 to 1).

*Clinical Findings*—Although there appears to be a characteristic clinical picture of meningococcemia yet a definite diagnosis cannot be made without positive blood culture for the organism. The picture has been ably described by Bloedorn<sup>16</sup>, Morgan<sup>5</sup>, and Dock<sup>14</sup>. The onset of the illness is usually sudden and is ushered in by a chilly feeling or a definite rigor, headache, malaise, fever and sweats. Following closely upon this are progressively increasing weakness, myalgia and arthralgia, a multiform rash, and an intermittent type of fever. The patient does not appear to be critically ill but has only a mild type of sepsis, with slight generalized glandular enlargement if any, slightly enlarged spleen, pain in the joints and slight limitation of motion because of the pain. The pulse continues to be rapid and often is out of proportion to the temperature.

In the great majority of cases the fever is present from the onset and although usually intermittent in character with rises every day or every other day it may in some instances be septic in type. In thirteen out of seventeen, or 76% of reported cases, the fever was intermittent and in the re-



maunder was septic. The average height of the fever is  $101^{\circ}$  F although it rose occasionally to  $104^{\circ}$  F. The leukocyte count is apt to vary with the fever, ranging from 11,000 to 24,000 per cu mm; however, when complicated by a meningitis it may reach 50,000 per cu mm or more. The leukocytosis is associated with a distinct rise in the polymorphonuclear ratio to 80% or more. The symptoms present during the febrile rise are not considerable and during afebrile periods the patient may feel perfectly comfortable. The fever may simulate the quartan or tertian types of malaria. Bloedorn<sup>10</sup> reports such an instance in a twenty-one year old patient, who had been ill for one week with headache, drowsiness, and just prior to hospitalization had a chill. Physical examination and all laboratory data for the first week were negative. He had a quartan type of temperature and then a septic course, with rises to  $102^{\circ}$  F and  $103^{\circ}$  F. He developed rose spots, arthralgia, and herpes, and on the eighteenth day positive blood cultures were obtained.

In most cases the arthralgia is not an exceedingly distressing symptom although it is almost always present. It consists of pain in the joints, usually of the extremities and is associated with tenderness over the bones and joints, and limitation of motion due to pain. The joints proper show very little or no destructive involvement, but in a few instances one joint did suppurate. When fluid is present in the joints the meningococcus may be isolated from them.

In all save two instances of the reported cases there was a multiform rash present varying from maculo-

papular, hemorrhagic, purpuric, petechial, erythematous, to those resembling the acute exanthems, erythema nodosum, erythema multiforme, rose spots, flea bites, toxic erythemas and even herpes. The lesions are proven to be embolic phenomena resulting from capillary hemorrhages into the skin producing local reactions. Fontanel<sup>17</sup> and LeBourdelle<sup>18</sup> report positive cultures of meningococcus from fragments of the skin taken from a purpuric rash. Brown<sup>19</sup> reports a case of meningococcus meningitis with lesions resembling measles which rapidly changed to large purpuric spots. Microscopic examination showed numerous intracellular and extracellular meningococci. The most common type of rash is maculo-papular occurring in greatest numbers on the extremities and found also on the trunk. The face and mucous membranes are free from the eruption. It is differentiated from erythema nodosum by the fact that the lesions are less painful and do not have a bluish border. The rash is usually associated with the arthralgia and occurs in crops with the rises in temperature, undergoing involution between febrile rises. The eruption may be extensive and in few instances may appear with the subsidence of the fever.

Except for the headache and slightly exaggerated reflexes, which may well be present in any sepsis, there are usually no symptoms referable to the central nervous system in this condition unless complicated by localization in the meninges. Lumbar puncture should not be done unless definite signs of meningeal irritation are present because of the danger of predisposing the meninges to infection. However, in the

presence of earliest signs of meningeal involvement lumbar puncture and intrathecal therapy should be instituted at once. In the case reported here no lumbar puncture was done.

Chronic meningococchemia may resemble other infections—most commonly malaria, rheumatic fever, subacute bacterial endocarditis, tuberculosis, undulant fever, typhoid fever, and secondary stage of syphilis. Differentiation is through laboratory procedures.

The most striking feature of this disease is the consistently positive blood culture, in all instances the organisms were isolated from the blood during the clinical course of the disease or at necropsy. During any phase of the disease, positive blood cultures may be obtained, but the organisms grow more rapidly from blood drawn at the height of the febrile rise than during afebrile periods as was demonstrated in this patient. It is frequently desirable to locate the focus of infection and since the naso-pharynx is the most common focus for this organism cultures from the naso-pharynx should be made. Smears and cultures from the naso-pharynx of our patient were positive, and remained so for some time after the blood cultures were negative, finally yielding to therapy directed at this site.

*Localization and Prognosis*—In a large percentage of cases localization has occurred in the meninges and heart although it has been reported to have occurred in the joints and nasal accessory sinuses. Eight of the seventeen reported cases of chronic meningococchemia showed localization. Five of

these developed meningitis, two of which terminated fatally, two developed a septic endocarditis, and one a septic endocarditis and meningitis combined, all ending in death. The prognosis in meningococchemia is altered by the associated complications. Analysis of the literature reveals that the prognosis in meningococchemia, uncomplicated, is good, death occurring in but 10% of the patients. Involvement of the endocardium makes the outlook very grave as all patients with this complication have succumbed. When complicated by meningitis fifty per cent in this series died.

*Treatment*—A great deal of controversy seems to exist in regard to the efficacy of specific serum therapy in the treatment of meningococchemia. Some authors have reported that the course of the disease was little affected by the use of serum, and a great many other measures such as foreign protein shock, fixation abscesses, autogenous vaccines, and others have been used but with even less striking results. In the cases of Mailowe<sup>13</sup> and the one here reported there was complete subsidence of all symptoms and a disappearance of the organisms from the blood as evidenced by repeated negative blood cultures. In both instances the serum used was found to agglutinate the organisms isolated from the blood. In our case the agglutination titer of the various commercial sera available was tested against the strain of meningococcus isolated and all sera showed the same titer—1 to 320. Serum sickness frequently occurs after the administration of serum.

## SUMMARY

1 A case of chronic meningococcemia without localization and followed by recovery is here reported

2 This is a relatively rare condition but has been more frequently recognized in the last few years

3 A definite diagnosis of meningococcemia can only be made by positive blood cultures for the organism

4. The prognosis is very good when no localization occurs.

5 In our case there was complete subsidence of symptoms and consistently negative blood cultures following the intravenous use of specific antimeningococcus serum

6 Meningococcemia offers an explanation for a limited number of cases of prolonged fever of obscure etiology

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# Non-Tuberculous Spontaneous Pneumothorax\*

## With Report of Cases

RALPH L. FISHER, A B, M D, *Detroit*

**S**PONTANEOUS pneumothorax, while occurring fairly frequently in tuberculosis, is a comparatively rare incident in other diseases. As a matter of fact, such authorities as Behier and Jaccoud claim that tuberculosis accounts for ninety per cent of the cases and there are some who even claim that all cases are due to a previous infection with the Koch bacillus. Browder<sup>1</sup> has reported a case with a ruptured sub-pleural abscess as the etiological factor. Lewald<sup>2</sup> has reported ten non-tuberculous cases with recovery of seven. Idiopathic cases have been observed by Kahn<sup>3</sup>, Weber<sup>4</sup>, Kelly<sup>5</sup>, Bedford and Joules<sup>6</sup>. Asthma as an etiological factor has been observed by Benedict<sup>7</sup> and by Emerson and Beeler<sup>8</sup>. A series of twenty-two cases of non-tuberculous origin occurring at the Mayo Clinic has been reported by Lemon and Barnes<sup>9</sup>. Stoloff<sup>10</sup> has recorded a series of cases occurring in infants and children as a complication of the following conditions: emphysema, apoplexy, gangrene of lung, pneumonia, pertussis, diphtheria, bronchiectasis, foreign body in lung, infarct, abscess of lung, typhoid and rupture of sub-pleural abscess.

Watson and Robertson<sup>11</sup> have reviewed two hundred cases of non-tuberculous spontaneous pneumothorax with a report of three cases. These three cases presented several interesting features. In one case during a five year period the patient had first a collapse of one and then of the other lung. Another case experienced two collapses eight months apart. A third case had fourteen collapses on the two sides and once a bilateral collapse. Physical and X-ray examinations revealed no organic pathology in any of these cases or in three other cases of spontaneous pneumothorax observed by these authors.

CASE No I—B G, white man, age 39, married, a laborer, entered the hospital complaining of severe pain in the chest. The family history is unimportant. The past history revealed that the patient had been subject to asthmatic attacks over a number of years and during the interval between attacks had had a slight cough. There was no history of recent loss of weight, hemoptysis, or night sweats. For the preceding six months he had tired very easily and experienced a slight shortness of breath upon exertion. Just previous to the onset of the present illness he had been suffering from a severe asthmatic attack. Four days previous to admission to the hospital just after going upstairs he suddenly experienced a severe pain in his right chest, had great difficulty in getting his breath and became very cyanotic. The pain and dyspnea had continued

\*From the Department of Medicine, Jefferson Clinic and Diagnostic Hospital

until time of admission, though not quite so severe

Physical examination showed the patient to be a middle aged man who appeared quite ill and had a rather anxious pinched expression to his face. Temperature was 97.8, respirations 35, and pulse 120. Blood pressure was 112 systolic and 80 diastolic. There was marked dyspnea. Mucous membranes

were pale and skin was loose. He was very undernourished. Pupils were equal and reacted to light and accommodation. Extraocular movements were normal. Eye grounds showed no abnormalities. Examination of the sinuses revealed a chronic purulent ethmoiditis. Tonsils were fairly large and pus could be expressed from the crypts. There was marked pyorrhea of the teeth. Thyroid



FIG 1 Radiograph of Case No I at time of pneumothorax

was negative. The chest examination revealed that the intercostal spaces on the right side were almost completely obliterated. Vocal fremitus and breath sounds were absent over the right chest. Breath sounds were accentuated over the left chest and many moist râles were heard at the left base. Cardiac dullness extended  $11\frac{1}{2}$  centimeters to the left of the midsternal line. The right border could not be made out. Pulse was very rapid, of rather poor quality, but regular. The liver border could be felt one finger breadth below the costal margin. Otherwise

physical examination was negative. Laboratory data showed a normal urine, a mild secondary anemia and negative Wassermann and Kahn reactions. X-ray revealed complete collapse of right lung.

This patient remained in the hospital a little over a month. His clinical condition gradually improved and he was discharged. About eight days after his return home he suddenly became very ill, was markedly dyspneic and cyanotic, and died within a short time.



FIG 2 Radiograph of Case No I three weeks after pneumothorax

CASE No II—This case was that of a young man, 29 years of age, single, and a physician by occupation. Family history negative. Past history revealed that he had frequent attacks of follicular tonsillitis when a student in college. There was a history of chronic otitis media on the right side and mumps and chicken pox when a child. Of temperate habits. No history of cough, night sweats or hemoptysis. Three months previ-

ous to present illness had an operation for acute mastoiditis on right side. Recovery was very slow, patient losing his hearing for three months. Was in a very run-down condition. One afternoon while walking down the street he felt a severe pain in his left chest and collapsed on the sidewalk. Respirations were very labored and pulse very fast, these conditions continuing until time of admission to the clinic.



FIG 3 Radiograph of Case No I four weeks after pneumothorax

Physical examination revealed a young man, pale, undernourished, very ill in appearance, and breathing with great difficulty. Temperature 98.2, pulse 130 and respirations 40. The other main positive physical findings were as follows: Coughing was frequent, motion in left chest very limited and intercostal spaces obliterated, absence of voice sounds and vocal fremitus on the left and no audible breath sounds, heart displaced to the right and pulse very rapid with occasional extrasystoles. Laboratory data were unimportant except for moderate secondary anemia. X-ray examination confirmed clinical diagnosis of pneumothorax of the left chest.

This patient very slowly improved, some respiratory embarrassment continuing for several years. It has now been seven years since his illness, and he is in perfect health. A recent X-ray examination revealed no pathology in lung.

CASE No. III (13) is that of a young man 30 years of age, occupation, clerk. Family and past history negative. Five days previous to onset of present illness patient, after cranking his car, experienced pain in his right shoulder. This pain was not very severe and continued until five days later, when out of doors he became cold and started to cough. At this time he felt a flutter-

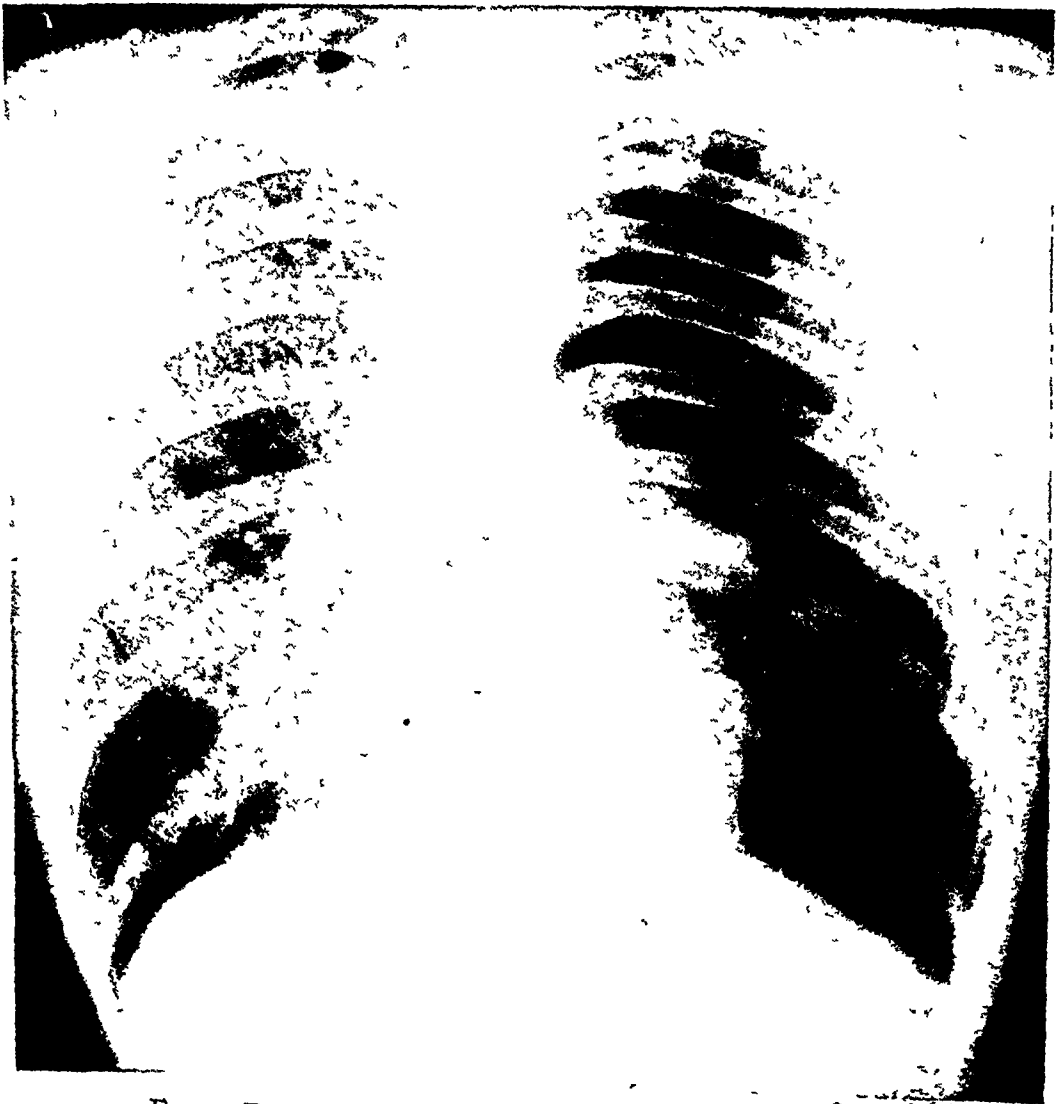


FIG 4 Radiograph of Case No. II at time of pneumothorax



ing sensation in his throat. He went to bed and remained there for several days. Two days later the cough re-appeared and it was very difficult to stop it. Breath became quite short at this time also. He remained in bed for a week during which time the cough and pain in shoulder persisted. Recovery was slow and uneventful over a period of three weeks.

Physical examination showed a fairly well nourished young man, coughing frequently and complaining of pain in the region of the right shoulder. Temperature was normal, pulse 100 but of good quality. Respiration was a little labored. Mucous membranes were pale. There was a slight enlargement of the cervical lymph nodes. The right chest showed a limitation of motion and obliteration



FIG 5 Radiograph of Case No II two years after pneumothorax

tion of intercostal spaces Voice sounds, breath sounds and vocal fremitus were absent over the right chest Physical examination otherwise was negative X-ray showed pneumothorax of right side

Physical examination of this patient three years later, other than a slight enlargement of the cervical lymph nodes and chronically

infected tonsils, is negative He has no symptoms of any respiratory trouble at present and is enjoying good health X-ray examination at present date is negative

Pneumothorax is a condition that is always secondary to a lesion of the lung or the structure with which it is

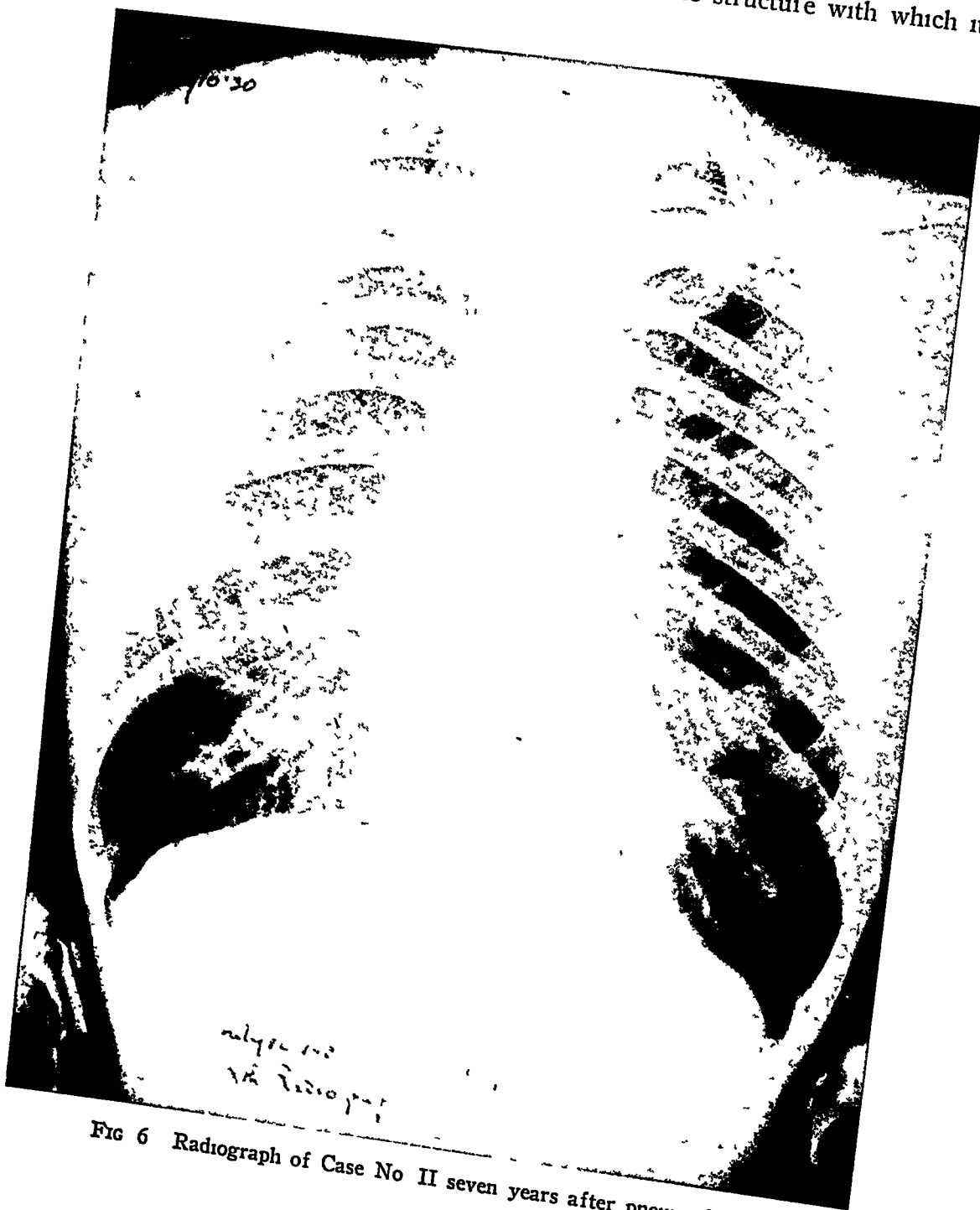


FIG 6 Radiograph of Case No II seven years after pneumothorax

enveloped According to the Hippocratic writings it was called empyema and it was not until 1759 that Meckel first recognized its significance insofar as respiration was concerned Its name was given to it in 1803 by Itard and in 1819 Laennec described a simple pneumothorax, pneumothorax with effusion and fistula Pneumothorax means gas in the pleural cavity This gas may be hydrogen due

to the action of certain bacteria; to nitrogen used as a therapeutic measure to collapse the lung; or air which enters the pleural cavity as a result of its exposure to the atmosphere By spontaneous pneumothorax is meant that type which occurs without any demonstrable provocative cause and naturally excludes those cases due to artificial means such as direct trauma and ulcerative communication between

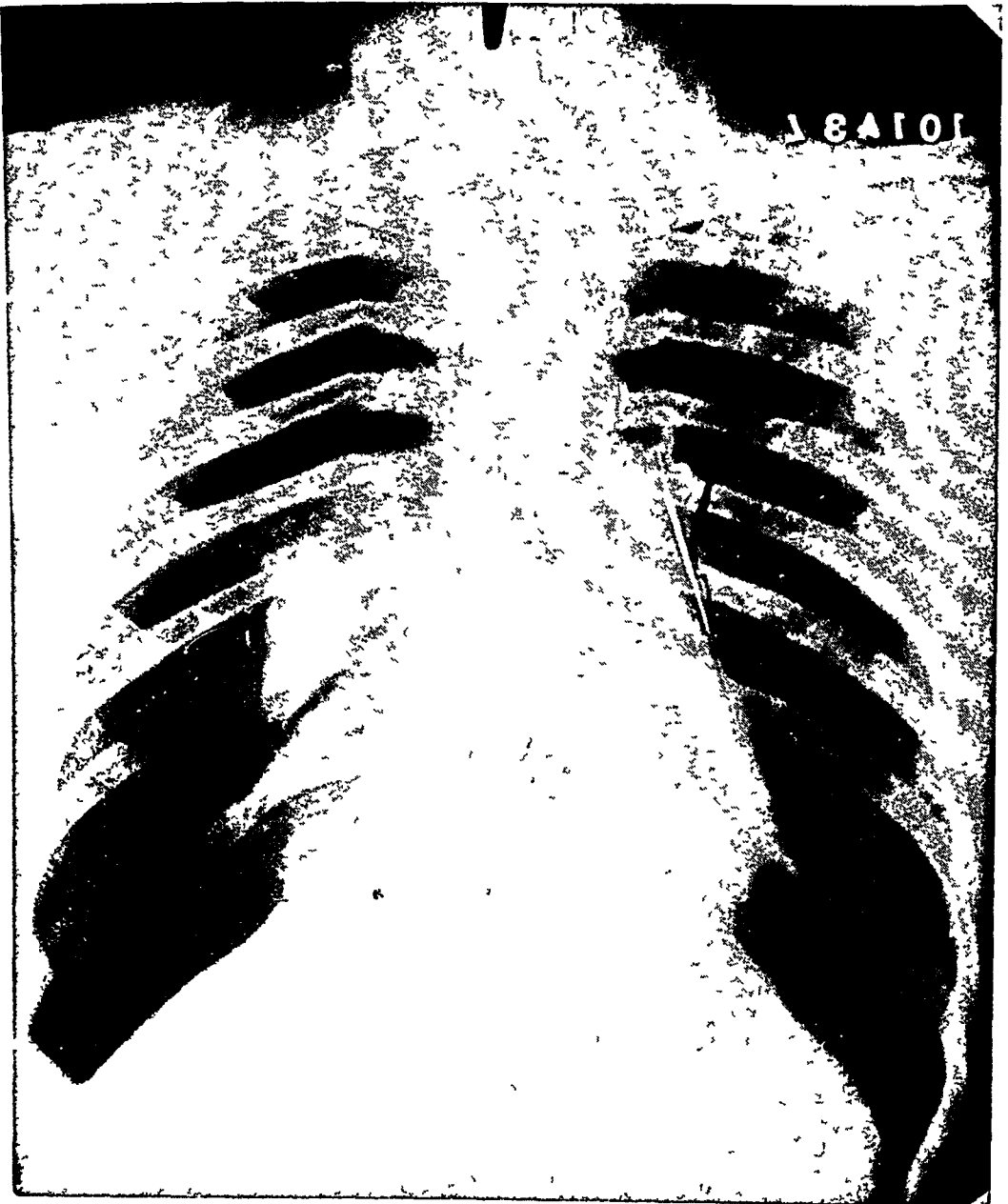


FIG 7 Radiograph of case No III at time of pneumothorax

the alimentary tract and pleural spaces. According to Hegner<sup>12</sup> the most common lesions in the tuberculous type are early small caseating tubercles just beneath the parietal pleura, small superficial tuberculous cavities and interstitial marginal or superficial emphysematous blebs not protected by pleuritic adhesions. So that "any sudden even slight increase in the intrapulmonary pressure or a slight uneven alteration of the pleural tension may cause rupture of the pleura and an

escape of air into the pleural space". Those cases due to asthma probably occur as a result of a rupture of an emphysematous bleb. Even normal lung tissue may rupture when subjected to great strain as occasionally happens in a paroxysm of whooping cough or during parturition.

According to the researches of Wint-  
rich and Weill, pneumothorax may be of three types: I, the valvular type, II, the open type; and III, closed pneumothorax<sup>14</sup>. The valvular type is the one

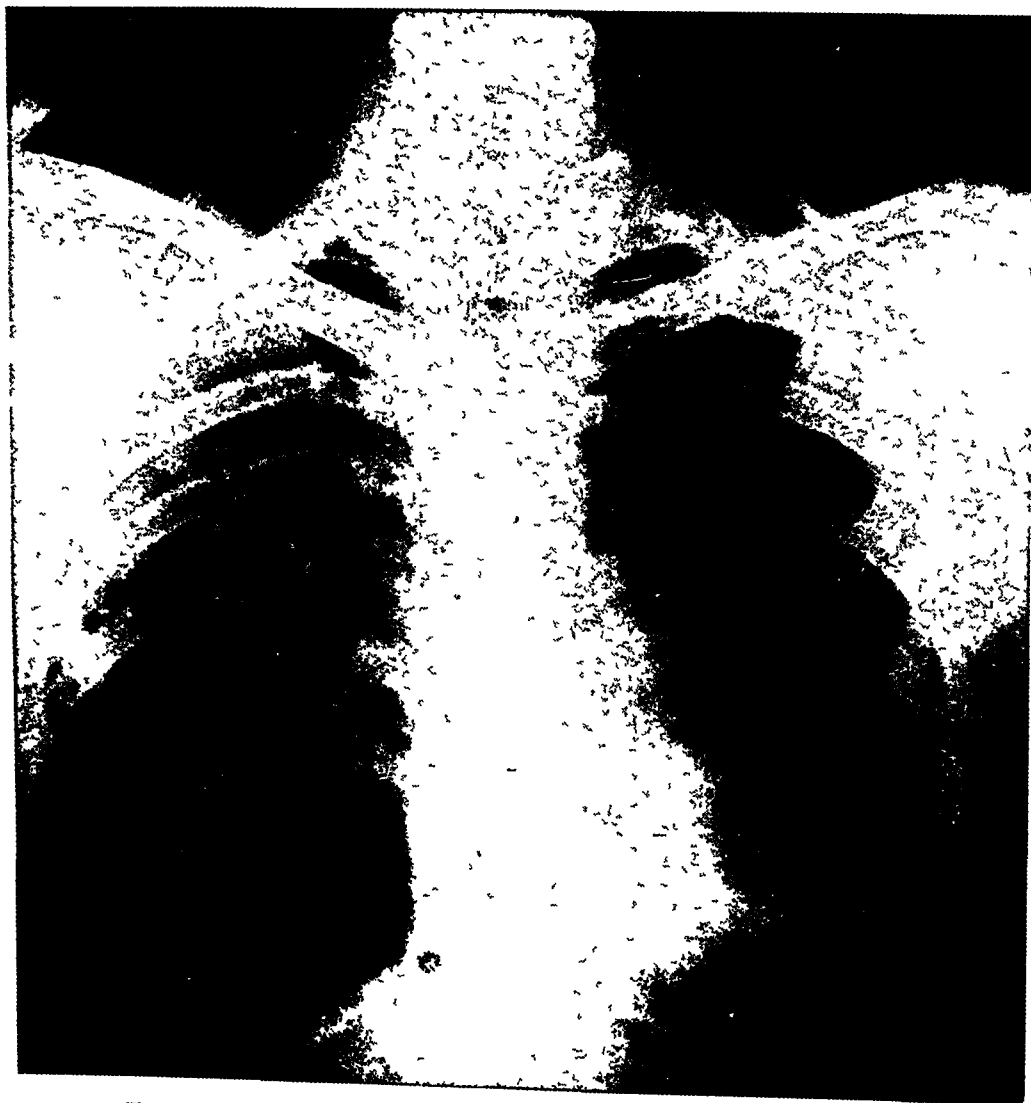


FIG 8 Radiograph of case No III two years after pneumothorax

usually encountered in spontaneous pneumothorax, the tissues in the vicinity of the tear in the pleura acting as a valve. Air then may enter the pleural cavity easily but is prevented from returning into the bronchial system. And air will continue to pass from the lungs into the pleural cavity until the intrapleural pressure equals that of the intrapulmonic. Thus during inspiration the intrapleural pressure becomes atmospheric pressure whereas during expiration the thoracic cavity collapses, the intrapleural pressure on the affected side exceeds the intrapulmonic, the mediastinum bulges toward the sound side, and the diaphragm on the affected side is depressed. The degree of dyspnea resulting from the collapse of the lungs depends on the functioning ability of the sound lung. It has been shown experimentally that an animal at rest can breathe with but one-tenth of its lung surface functioning without experiencing dyspnea. The sudden pain which usually ushers in the pneumothorax is due to the laceration of the pleura. Similarly the cough is due to pleural irritation and is usually unproductive. The extent of collapse of the lung depends upon the presence or absence of adhesions.

The symptoms of pneumothorax are more or less uniform. It is usually ushered in with acute stabbing pain, sometimes diffuse and sometimes localized, and at times radiating toward the abdomen or spine. As a rule, severe dyspnea accompanies the pain and the patient assumes a sitting posture. He appears anxious, there is cyanosis of the lips and he is covered with perspiration. At first cough is absent and

expectoration is tardy. The pulse is faint and about 120 a minute. The extremities are cold and the temperature may range from 102.2 to 104. Death may occur in several hours, depending upon the functioning ability of the other lung. The dyspnea and other signs of shock gradually disappear, though they may persist for as long as two weeks in the invalid.

The physical signs are characteristic. The affected side is almost immobile, the intercostal spaces are filled and are permanently dilated. Vocal fremitus is abolished on the affected side. Percussion reveals an increase in resonance which may be tympanic or even amphoric. Auscultation reveals a complete absence of vesicular sounds. There is so-called respiratory silence. Such physical signs as the metallic tinkle of Laennec and the coin sound of Trousseau may be present.

The X-ray findings are exceedingly important. They show in general an enlargement of the hemithorax "with excessive clearness of the pulmonary field so that the shadows of the ribs and intercostal spaces are hardly distinguishable." The collapsed lung may be seen back against the vertebral column and casting a gray shadow. The diaphragm is either lowered or flattened and practically immobile. The mediastinum may be attracted toward the pneumothorax during inspiration.

Insofar as prognosis is concerned, there are two clinical types. I, the rapidly fatal, and II, the non-fatal. In the former death usually occurs within a few hours, whereas in the latter a course of gradual improvement ensues, the air absorbing within five or

six weeks Recovery may occur in twelve or fifteen days The outcome also depends upon whether or not there are any complications such as hydro-pneumothorax, pyopneumothorax, etc It has been estimated that 75% of the cases eventually are fatal

Treatment should be divided into two heads I, immediate, and II, during the course of the condition Immediate treatment consists mainly in relieving the pain with opiates, allaying the cough, and general constitutional measures for the shock If it is of the suffocating type, decompression of the lung, mediastinum and heart may be necessary If the pneumothorax remains, fluid is quite apt to develop, in this case withdrawal of the fluid if it becomes abundant and injections of nitrogen are measures to be followed In case the fluid becomes pus, it may be even necessary to do a

thoracotomy Later, blowing into bottles may help re-expand the lung

### SUMMARY

(1) A hasty review of the literature is given

(2) Spontaneous pneumothorax is reported in one case with asthma as causative agent In a second case no cause was apparent In a third case physical exertion seems to have had an etiological bearing upon its occurrence

(3) Symptomatology, physical signs and treatment of pneumothorax are discussed

(4) The impression is gained that idiopathic spontaneous pneumothorax is of much more frequent occurrence than is generally recognized

(5) These cases give further support to the contention that spontaneous pneumothorax is not necessarily secondary to infection with tuberculosis

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# Cardiac Overaction

## The Most Constant and Most Dependable Sign in Thyroid Toxicity\*

By HENRY J VANDEN BERG, M D , F A C S , *Grand Rapids, Michigan*

**T**HE heart seems to be the first organ to show definitely the effects of thyroid toxicity. With this statement everyone seems to agree. This toxicity is manifested early in the heart action in that the rate is accelerated and the force of the beat is increased. Acceleration of the heart rate is one of the most common physical signs one meets in clinical medicine, whereas cardiac overaction occurs in comparatively few conditions. It may be presumed that all organs and tissues are affected by thyroid toxicity, but none can be so advantageously measured and studied as the heart, both because of its position and because it is constantly in action. No other organ likewise affected will so early produce definite symptoms directed to itself.

Since thyroid toxicity does manifest itself so early in misbehavior of the heart, it naturally follows that the detection of any alteration from the normal in heart action is very important.

In my experience, cardiac overaction in thyroid toxicity is a more constant sign than rate acceleration. It is, in fact, the most constant single sign in goiter toxicity, and it is one of the

earliest. Because of this, its importance should be emphasized, but it is not. The sign, when referred to in the literature, is mentioned, as a rule, in the most casual way. It oftentimes is not mentioned at all.

Cardiac overaction is to be elicited by (a) palpitation, and (b) auscultation.

### PALPATION

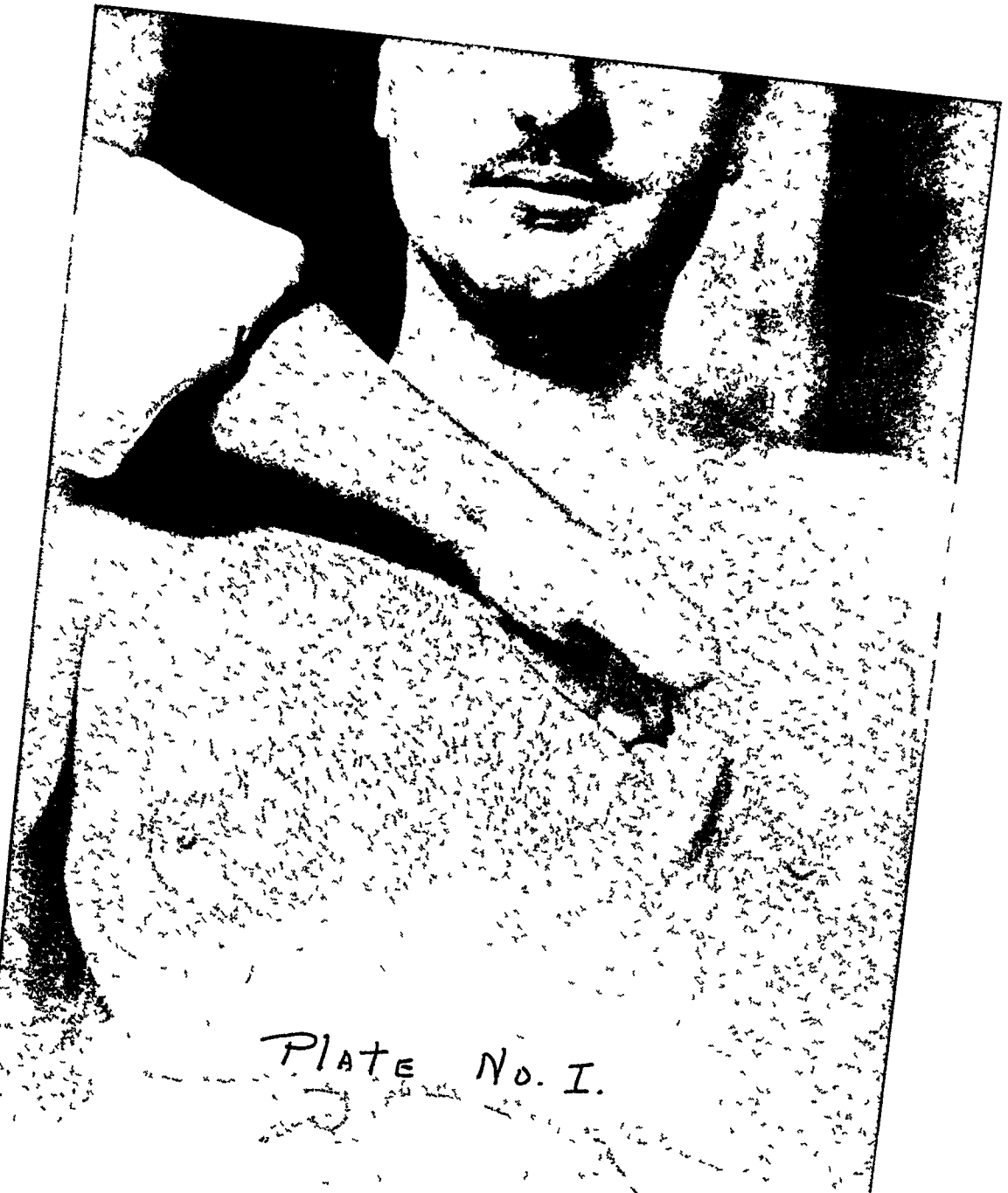
In palpation the technique is important if any one is to get the greatest possible assistance from its use\*. The inner aspect of the hand should be used (see Fig 1), not the palm, and it is obvious that a light hand should be practiced. In thyroid toxicity both the right and left heart are in a state of overaction, consequently the increased impulse will be present over the entire precordial area and usually for a variable distance beyond. The distance beyond will depend upon the intensity of the overaction and it naturally will be altered in the presence of a thick, heavy wall and more so if emphysema is also present. The impulse is a quick, sharp slap or thrust. It is quite different from that in overaction that occurs in hypertension. In

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\*From the Grand Rapids Clinic

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\*For this technique I am indebted to one of my teachers, Prof Kovacs of Vienna





the latter the impulse to the palpating hand is comparatively long, slow and heaving, and it is confined, in a well compensated case, to the left heart. Overaction of the hypertension type is best elicited by using the tips of the fingers.

### AUSCULTATION

There is a normal intensity relation between the first and second heart sounds with which one should be perfectly familiar if he is to detect slight variations from the normal. The normal first sound is long, more or less loud, and low pitched, the second sound is shorter, less loud and higher pitched. Under thyroid toxicity the character of the heart sounds changes. The first sound becomes shorter, louder and higher pitched, rather soon the pitch becomes as high or higher than that of the second sound. The degree of variation from the normal is dependent upon the degree of toxicity and perhaps somewhat upon the length of time of toxicity. For the purpose of convenience, and of one's records, cardiac overaction can be divided into four grades—for example, overaction grade I, overaction grade II, and so on. In a goiter, then, that is definitely toxic, one will be impressed by the first sound being quick, short, loud and snapping.

It is interesting to note the change in the intensity of the heart action during the pre-operative management. It calms down materially in nearly every instance, quite in keeping with the general improvement. It is furthermore interesting to note the change that follows surgery. In some cases the character approaches the normal almost immediately—in a day or two, in

others it will be a matter of a week or weeks, or even a few months. Cases in which a slight degree of overaction persists are those which are still somewhat toxic. *Thus overaction is the best clinical criterion or measure to go by to determine the presence of remaining toxicity.* Palpation, of course, goes hand in hand with auscultation.

Cardiac overaction of the thyroid type does occur in conditions other than in toxic goiters. They are (1) excitement (temporary), (2) mitral stenosis, (3) anemias; (4) fevers.

### EXCITEMENT, (temporary)

The nervous, supersensitive type of individual will often have, especially when first seen, acceleration of the pulse rate, an increase in the force of the heart beat (thyroid, in type), and other signs that resemble those seen in mild thyroid toxicity. Since a very considerable percentage of patients are of this constitution, the question of differentiation between a simple supersensitive reaction and a superimposed mild thyroid toxicity confronts one almost daily. If, after leaving such a patient to rest for half an hour or so, the heart does not quiet down, the question of a thyroid factor demands further observation and study (metabolism determination, and so forth).

### MITRAL STENOSIS

Upon both palpation and auscultation the well compensated heart of mitral stenosis may resemble very closely the behavior of a toxic goiter heart. There are, however, distinguishing points that make it possible to make the differentiation. A thrill may be present in both, but much more fre-

quently in mitral stenosis. The most helpful point of differentiation is the timing of the thrill which may, of course, become difficult in a very rapid heart. The presence of a thrill is best made out with the palm of the hand. Murmurs, if present, are likewise differently timed, systolic in the case of pure hyperthyroidism and of course, diastolic in mitral stenosis. Secondary signs such as an accentuated second pulmonic sound, the usual small pulse in a well compensated case of mitral stenosis, and the large pulse pressure in cases of hyperthyroidism, afford evidence that is helpful in arriving at a diagnosis. It must always be borne in mind that the two conditions may be simultaneously present. If a suspected thyroid factor in the case of mitral stenosis cannot be finally eliminated, the patient should be given the benefit of the doubt and accordingly should be advised to have the thyroid removed, since it can be done with a great degree of safety. The same principle and reasoning should obtain in all cardiac cases in which the question arises, and more especially so if an adenoma is present. It will be surprising what such management may, in certain cases, hold in store for a patient.

#### ANEMIA

The cardiac overaction of a patient who is very anemic resembles very closely the cardiac overaction of a toxic goiter patient. There are, however, some detailed conditions which serve to differentiate one from the other. Upon auscultation the first sound over the apex is not quite so loud and snapping as in the case of a thyroid heart. Moreover, a systolic murmur which is

usually present in these conditions is longer and softer in the case of anemia. There is no difference to the palpating hand. At any rate, by proper evaluation of all the available clinical and laboratory data there should be little, if any, trouble to differentiate cardiac overaction of anemia from that of thyroid origin.

#### FEVERS

In fevers the heart action is increased in intensity along with the rate acceleration, but again one should have little difficulty in making a diagnosis. If the impression is gained for one reason or another that a thyroid factor is present in a patient with temperature, it obviously follows that the suspicion must be disposed of in an orderly fashion.

In citing and discussing the exceptions above it may strike one that they are so numerous, complicated, and confusing that the sign of cardiac overaction in goiter toxicity loses much of its value. In reality the diagnosis of cardiac overaction is not difficult for one accustomed to making clinical examinations. It does, however, necessitate the skillful use of one's sense of feeling and hearing. In this connection I wish to commend an article recently published by Dr. James B. Herrick\*\* in which he makes a plea in defence of the stethoscope and warns against its use becoming a lost art.

One can sum up the entire question by saying that first of all painstaking attention should be given to the study of the heart of every case examined.

\*\*HERRICK, JAMES B. "In Defense of the Stethoscope." *Annals of Internal Medicine*, p. 113, August, 1930.

Valuable clinical data will be derived from this practice. If it is continued year in and year out, slight variations from the normal will be detected almost instantaneously. If anything abnormal is detected, such study as is necessary can then be given it. If overaction is present, one can in a few moments make a mental survey of the conditions in which overaction occurs. They are after all few. By evaluating the characteristics of each, one should be able to determine with a reasonable degree of accuracy of what such overaction is an expression. One must always keep in mind that two, or even more conditions, may be present simultaneously. In the majority of instances the overaction will be found to be of

thyroid origin, at least in a goiter district.

The point I wish to emphasize is the presence of cardiac overaction at a time when the symptoms and signs generally understood to express thyroid dysfunction, are not yet obvious—in other words, in very early or mildly toxic cases\*\*\* and in atypical cases. The sign is valuable also after operation as being an indication of remaining toxicity. Because of its presence and constancy in practically all cases of goiter toxicity, it has been to me, for a number of years, the most helpful sign suggesting the presence of thyroid dysfunction.

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\*\*\*VANDEN BERG, HENRY J. "How Long is a Toxic Goiter Toxic?" *Western Journal of Surgery*, 1930

# The Pituitary and the Suprarenal Cortex Glands as Related to Pigment Formation\*

By ROBERT C MOEHLIG, M D, *Detroit, Michigan*

THE remarkable correlation of function between the various endocrine glands shows how well Nature has endowed our bodies with a complex mechanism. The unfolding of these correlations gives us an insight into many obscure problems.

For some time I have been working along embryological lines in order to solve some of the correlations. It is quite natural to look for a solution in embryology and much data have been supplied to support this hypothesis.

One of the most definite correlations is that of the pituitary gland and suprarenal cortex. In this particular correlation, we are treading upon firm ground, for we have clinical, pathological, experimental and embryological facts which prove beyond question that the state of the pituitary gland is shown by a similar state of the suprarenal cortex. Other articles<sup>1</sup> have shown that the embryohormonic relation of the pituitary to mesodermal tissues gives a clear-cut and logical explanation of the suprarenal cortex involvement, as the latter is a mesodermal tissue. The basis for these statements is found in hypo- and hyperplastic states of the pituitary which result in a

concomitant hypo- and hyperplastic state respectively, in the suprarenal cortex. Experimental work duplicating these clinical states of the pituitary, likewise produces the same concomitant condition in the suprarenal cortex. Cushing<sup>2</sup> agrees that the suprarenal cortex defect accompanying anencephalic states is unquestionably attributable to the absence of the pituitary. He goes on to say "It is interesting in showing this influence is present even in embryonic life, for I assume it is an experiment on the part of Nature comparable to what we may produce during life in the laboratory by extirpation of the hypophysis." We may safely say, then, that the state of the pituitary from a functional standpoint, carries with it a concomitant change in the suprarenal cortex. Aplasia or atrophy of the pituitary results in an aplasia or atrophy of the suprarenal cortex and the same holds true for the hyperplastic states. It is to be emphasized that the suprarenal medulla, an ectodermal tissue in contrast to the mesodermal cortical tissue, is not affected by the state of the pituitary. While this correlation provides an understanding for many problems such as cholesterol metabolism and related con-

\*From the Department of Internal Medicine, Harper Hospital, Detroit

ditions, it is the purpose of the present article to apply the fundamentals of this correlation to pigment formation

Concerning the chemical mode of action on pigment and pigment cells of the pituitary and suprarenal cortex secretions, I can add nothing. But I hope the embryohormonic relations of the pituitary to mesodermal tissues as previously and herein given, will stimulate research by physiological chemists

Assembled data has shown

- 1 That posterior lobe pituitary extract is a melanophore stimulant

- 2 That the suprarenal *cortex* occupies a high position in the physiological pigment production

- 3 That the pituitary gland affects particularly mesodermal tissues

We note from this that the pituitary gland and suprarenal cortex, which we know are definitely correlated, are concerned with the problem of pigment formation

It has been known for some time that posterior pituitary extract is a melanophore stimulant. Smith<sup>3</sup>, Allen<sup>4</sup>, Spaeth<sup>5</sup>, Hogben and Winton<sup>6</sup>, Swingle<sup>7</sup> and others have shown the stimulating effect of posterior pituitary extract on skin melanophores. Smith<sup>3</sup> has done some excellent work on pigment changes in hypophysectomized tadpoles. These tadpoles become silvery white and Smith showed that the color changes are due to hormone action by affecting reciprocal epidermal transplants between "albino" and normal tadpoles. The chromatophores of the skin thus transplanted quickly assume the state of contraction or expansion characteristic of the corresponding cells of the host

Only posterior pituitary extract produces a permanent darkening of the "albino." Of importance in Smith's work are his findings of a diminished suprarenal cortical material in the hypophysectomized "albino."

Hogben and Winton<sup>6</sup> have shown that the action of the extract must be upon the pigment cell itself, as it acts upon the melanophores after paralysis of the nerve endings. Rowe<sup>8</sup> working with "pitressin," a solution of the pressor principle isolated by Kamm and his associates, found that it stimulates frog melanophores.

Injection of posterior extract produces an expansion and darkening of the melanophores. Extract of one frog's hypophysis is sufficient to darken twenty to forty frogs (Trendelenberg<sup>9</sup>).

The pigment cells of the frog iris expand and darken when immersed in posterior lobe extract.

An explanation of the melanophore effect of posterior extract may be found in embryological studies. The purpose would be to determine the embryological origin of the melanophores.

Bloch<sup>10</sup> and his associates have studied the problem of pigment formation with particular reference to the embryological origin of the skin pigment cells. He defines melanoblasts as those cells which are capable of forming pigment, while those containing pigment which they themselves have not elaborated but have obtained elsewhere, (absorbed or phagocytized) are called chromatophores or melanophores. The mesodermal part of the skin, the corium, contains in man and in certain higher mammals, two entirely different kinds of pigmented cells. One

type are connective tissue cells which have phagocytized pigment which was originally formed in the epidermis. Another type which is found in the cutis, are the mesodermal melanoblasts, which he calls "Mongol" cells. They elaborate their own pigment, entirely independently of the epidermal pigmentation and embryologically long before this latter has appeared.

He says that the so-called blue nevi are large or circumscribed moles, which differ from ordinary brown moles in their blue color. As the cells of these blue nevi are mesodermal melanoblasts, the malignant growths which originate from these moles, are therefore true melanosarcomata.

Ribbert<sup>11</sup> many years ago was the greatest defender of the view that connective tissue gives off pigment cells and likewise believed that the nevus elements and melanotic pigment in general are derived from chromatophores and therefore are mesodermal in origin and that these cells stand in direct physiological relation to pigment formation. Borst<sup>12</sup> likewise supports this view. Naturally the relationship of physiological pigmentation is interesting in regard to melanotic tumors.

My purpose is to bring into physiological relationship the pituitary gland and the mesodermal pigment cells. Bloch<sup>13</sup> gives as his opinion that the melanophores of the frog are mesodermal in origin. Ewing<sup>14</sup> says "The evidence accumulating in recent years from the comparative study of the physiology of the color function in the animal kingdom is a very formidable argument in favor of the specific mesoblastic nature of the chromatophores." With this evidence at hand, the em-

bryohormonic relation of the pituitary to mesodermal cells, provides a self evident explanation for its melanophore effect.

It affects specifically mesodermal cells and therefore the darkening effect of the mesodermal melanophores by the extract is explained. By the same token, the "albinous" effect of hypophysectomy is also explained.

The suprarenal cortex, correlated with the pituitary gland, which as we have seen affects pigment cells, occupies a high position in physiological pigment formation. Such studies force one to the conclusion that pigmentation is a metabolic phenomenon.

Jaeger<sup>15</sup> studying melanosarcoma in grey horses had made some interesting observations on pigment formation. He found that melanosarcoma attacked practically only those horses whose hair had been either black or brown and then turned grey. He says that of great interest is the influence of the suprarenals on pigment formation. He is of the opinion that the suprarenal cortex, and particularly the cells of the zona fasciculata are responsible for the typical melanin formation. It has been shown by experiments that melanin production is a product of the suprarenal cortex. It has usually, but erroneously, been believed that the melanin is a product of the suprarenal medulla and chromaffin system.

It has been found that the epidermis of the grey horse is light in color, as well as the hair itself, so that there seems to be an intimate relationship between pigment effects of the body covering and the predisposition to melanosarcoma. In his studies on horses he finds that in melanotic sar-

coma there is a paralleling of the two processes, viz a proliferation of connective tissue and fibroblast cells and an enlargement of the suprarenal cortex

-- Melanosarcoma of the grey horse is an expression of a metabolic anomaly. Jaeger believes an abnormal pigment metabolism is present which releases the specific "melanogen" ferment producing an intracellular oxidation by means of the suprarenal cortex ferment. There is a conversion of the melanin by suprarenal cortex substance. Parallel factors are at work, pigment changes and the cell hyperplasia.

Ewing<sup>14</sup> says "It follows that there must be a close parallel between physiological formation of pigments and that seen in pathological conditions, such as melanosarcoma. Much evidence has been collected which points to the metabolic origin of pigment."

From the data at hand, it is evident that the suprarenal cortex is a factor in pigment production. The chemistry and its mode of action, are still unsolved. We have, therefore, two glands that are concerned with pigment formation, the pituitary which has an embryohormonic effect on mesodermal tissues, and the mesodermal suprarenal cortex, which mirrors the state of the pituitary.

The embryohormonic relationship between the pituitary gland and the suprarenal cortex leads us into the study of physiological pigment formation and that seen in tumor pigment formation.

Certain clinical facts furnish interesting proof of the pituitary and sup-

rarrenal cortex influence on pigment formation.

The darker races, such as the negro, should have a more active pituitary than the Caucasian, accepting this in the sense of the race as a whole. The negro, should also show, by the same reasoning, a more active mesodermal tissue involvement. His constitutional make-up should show a greater vulnerability of the mesodermal "anlage." Therefore hypo- and hyperplasia of these tissues with resulting clinical symptoms should be very common in the negro.

The mesodermal suprarenal cortex, mirroring the state of the pituitary, is found to be much larger in the negro (Jaeger<sup>15</sup>). Is this why the negro seldom has "Addison's disease?"

Connective tissue, another mesodermal tissue, shows a greater overgrowth in the negro and the tendency to keloid formation is also well known.

We are well aware of the fact that neurofibromata originating in the mesodermal fibroblasts are a very frequent finding in acromegaly (Von Recklinghausen's disease).

The mesodermal dentin and cementin accounts for the excellent formation of the teeth, for which the negro race is famed. The overgrowth of the mesodermal smooth muscle, as in the uterus, may account for the high incidence of fibroids in this race. The mesodermal sex glands are notoriously well developed in the negro. The early maturity of the darker races and the supposedly greater libido of these races could be understood from this. The predisposition of the negro race to luetic aortitis (mesodermal blood vessels) is also common knowledge.

Then too, in acromegaly and gigantism, we find telangiectasis (mesodermal blood vessels) (Grunfeld<sup>16</sup>, Bigler<sup>18</sup>, Lehman<sup>16</sup>) and also abnormal pigmentation of the skin. Uebelin<sup>16</sup> notes the frequent formation of tumors in the skin of acromegalics.

Further argument of the negro race's mesodermal vulnerability is shown by the fact that this race has an affection strictly limited to them. I refer to the involvement of the red blood cells in sickle cell anemia. Negroes, on the other hand, seldom have pernicious anemia.\*

It is interesting that with such a high incidence of syphilis, paresis and tabes are not as frequent in the negro as in the Caucasian race. This again demonstrates that the ectodermal system is not so vulnerable.

The mesodermal bone tissue frequently shows abnormalities. Gigantism, dwarfism, rickets and achondroplasia are often met with in negroes, the dwarfism being characteristic of the pigmy race in Africa. It is a well known fact that the Caucasian race, when acromegaly develops, takes on the coarse features and characteristics of the negro tissues.

It would be interesting to see if acromegaly ever develops in the blond and if so to note the change in hair and skin pigment. The hair papilla and outer sheath are of mesenchymal origin and influenced therefore by the pituitary gland. The marked hairiness of the acromegalic is understood on this basis, as well as the lack of hair in the hypopituitary individual.

\*Ewing says he has never seen melanoma in a negro (Personal communication).

In hypopituitarism in contrast to hyperpituitarism, the skin is poorly pigmented and the effects of the sun rays and other actinic influences are much more severe in these people.

It follows that hyperpituitary individuals should have many pigment anomalies of the skin and iris. This is true clinically. The negro of course has a darker sclera than the white race. The ophthalmologists could solve many eye disturbances if attention was paid to the embryological origin of the layers of the eye with reference to the selective action of the pituitary on mesodermal tissues and particularly to mesodermal pigment diseases. Such fundamental studies become of greatest importance to medical progress.

From what has gone before it becomes almost an inevitable corollary that the pituitary gland and suprarenal cortex are the responsible factors for the pigmentation of pregnancy. The pituitary forms at this time the well known "pituitary of pregnancy," and the suprarenal cortex becomes hyperplastic during pregnancy.

The embryohormonic relations of the pituitary to mesodermal tissues give a most rational explanation of pigment formation and a most reasonable explanation for many pigment changes.

#### SUMMARY

Both the pituitary gland and the suprarenal cortex are concerned with pigment formation. The embryohormonic relations of the pituitary to mesodermal tissues explains the melanophore action of posterior lobe extract. The mesodermal suprarenal cortex, reflecting or mirroring the state of the pituitary is also concerned with



pigment formation The negro race with a comparatively more active pituitary gland is constitutionally predisposed to disease affecting mesoder-

mal tissues The pituitary gland and suprarenal cortex are probably responsible for the pigmentation of pregnancy

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# Thoracic Aneurysm

## Statistical Study of Seventy-one Cases\*

By SHELTON P. SANFORD, A. M., M. D., *Atlanta, Ga*

THE object of this paper is to present a statistical study of cases of aneurysm of the thoracic aorta at the Grady Hospital, Emory University Division. A series of seventy-one was selected. Necropsy was performed in thirty-two of these. A number of cases have been discarded because the diagnosis seemed uncertain and necropsy was not done. All patients were colored.

The seventy-one cases have been studied with regard to the following twenty-two points

- 1 Age
- 2 Sex
- 3 Admission Diagnosis
- 4 First Symptom
- 5 Chief Complaint
- 6 Duration
- 7 Initial Lesion
- 8 Wasserman Reaction
- 9 Roentgenograms
- 10 Aortic Second Sound
- 11 Cardiac Irregularities
- 12 Abnormal Pulsations
- 13 Inequality of the Pulse
- 14 Blood Pressure
- 15 Hoarseness
- 16 Dysphagia
- 17 Tracheal Tug
- 18 Hemoptysis
- 19 Inequality of the Pupils
- 20 Glandular Enlargement
- 21 Cause of Death
- 22 Necropsy

(1) *Age* The youngest of the group was 22 and the oldest 80. Arranged according to age there is a rise at 40 which represents the age of greatest frequency of disability from aneurysm. There is a rapid fall to 50. After 50 there are only sporadic cases up to the age of 80. The average time interval from initial lesion to onset of symptoms is slightly over fifteen years. There is also a small peak at 26. I believe this peak probably represents cases of acute syphilitic myocarditis associated with small aneurysms of the sinuses of Valsalva. This group will be made the subject of a separate paper.

(2) *Sex* In the series of 71 cases there were 54 men and 17 women. This proportion of women is larger than in textbook statistics. It includes perhaps, a few cases of non-syphilitic rupture of the aorta.

(3) *Admission Diagnosis* An analysis of the diagnoses on admission in proved cases of aneurysm has been made in an effort to point out some of the pitfalls of diagnosis. In 30 of the series the correct diagnosis of aneurysm was made. The diagnosis of aortic regurgitation was made nine times. This was usually done on the murmurs alone. When murmurs simulating aortic regurgitation exist with-

\*From the Emory University Division, Grady Hospital

out a Corrigan pulse, low diastolic pressure and other peripheral signs of aortic regurgitation, one should strongly suspect aneurysm. Three cases were diagnosed pulmonary tuberculosis. An examination of the blood pressure would have helped exclude this error. Most cases of pulmonary tuberculosis show a systolic blood pressure of 110 with a diastolic of 70 or lower, while cases of aneurysm with pressure on the trachea show higher pressure until the last stages of the disease. One case was diagnosed chronic adhesive pericarditis, probably on account of murmurs.

TABLE OF ADMISSION DIAGNOSES

Aneurysm	30
Aortic Regurgitation	9
Mediastinal Tumor	3
Pulmonary Tuberculosis	3
Hypertension	2
Bronchitis	2
Cardiac Asthma	1
Mitral Stenosis	1
Aortic Stenosis	1
Pneumonia	1
Carcinoma of Lung	1
Laryngeal Obstruction	1
Syphilitic Heart Disease	1
Auricular Fibrillation	1
Syphilitic Aortitis	1
Tuberculous Laryngitis	1
Congestive Heart Failure	1
Tabetic Bladder	1
Dementia	1
Acute Alcoholism	1
C N S Syphilis	1
Duodenal Ulcer	1
Peritonitis	1
Chronic Adhesive Peritonitis	1
Cirrhosis of Liver	1
Renal Calculus	1
Osteomyelitis	1
No Diagnosis	1

The correct diagnosis was the most frequent one. In some of the other cases two conditions coexisted and the

symptoms produced by the aneurysm were negligible or entirely overshadowed by an acute disease. By an examination of the table it is seen that in 31 of the incorrectly diagnosed cases the symptoms were cardiorespiratory and directly attributable to the aneurysm. In 4 cases the outstanding symptoms pointed to the central nervous system and in 3 of these the immediate cause was the aneurysm. In the fourth paresis coexisted. In the remaining, aneurysm was incidental to other diseases.

(4) *First Symptom* The first symptom of the illness leading to the diagnosis of aneurysm was investigated in 68 cases. The distribution was as shown in the following table.

Pain in chest	25
Dyspnea	23
Cough	8
Dysphagia	3
Palpitation	1
Asthma	1
Enlarged gland	1
Vertigo	1
General malaise	1
Hoarseness	1
Convulsions	1
Syncope	1
Ascites	1

The table needs little comment. In a large majority, 61, of the cases the first symptom directed attention to the chest.

(5) *Chief Complaint* The presenting symptom was examined in 70 cases.

Dyspnea	29
Pain	22
Dysphagia	3
Tumor	2
Cough	2
Angina	1
Asthma	1

Hoarseness  
 Unconscious  
 Acute retention urine  
 Dimness of vision  
 Dementia  
 Abdominal cramps  
 Osteomyelitis  
 Epistaxis  
 Ascites

1 of the series There was sufficient  
 2 abnormality present at least to sug-  
 1 gest aneurysm in 47 No examination  
 1 was made in 10 In 14 cases there was  
 1 no reason to suspect aneurysm by  
 1 roentgenograms alone It must be re-  
 1 membered that small aneurysms situ-  
 1 ated in the pericardium will not be  
 shown roentgenographically It is this  
 group which gives the greatest trouble  
 in diagnosis and is usually found only  
 at necropsy

In 61 of the 70 cases the chief complaint was one which should have directed attention to the cardiorespiratory system In 5 the presenting symptom suggested a C N S lesion In 4 of these the aneurysm was responsible for the symptomatology In 4 the presenting symptom was such that the diagnosis was not even remotely suggested

(6) *Duration* The duration of symptoms before fatal termination was investigated in 40 cases It varied from one day to seven years, but in the majority of cases death followed within three months after the onset of symptoms

(7) *Initial Lesion* In 35 cases of the series a definite history of an initial lesion, with adenopathy was obtained, and the shortest period between the primary sore and the earliest symptom suggesting aneurysm was two years, the longest was 50 The average in the 35 cases was 15 years

(8) *Wasserman Reaction* The Wasserman reaction on the blood was positive in 50 of the 71 cases, negative in 11 and not mentioned in 10 This represents a positive Wasserman reaction in 82 per cent of the cases where the test was reported

(9) *Roentgenograms* A roentgenographic examination was made in 61

(10) *Aortic Second Sound* There has been much written about the accentuation of the aortic sound in syphilitic aortitis and aneurysm It is recorded as present in 37 of this series, replaced by murmur in 8, absent in 8, and not mentioned in 18 In our experience, in the absence of well marked hypertension, an accentuated aortic second sound is a most reliable sign of aneurysm Fortunately, when hypertension and aneurysm coexist, other signs help to make the diagnosis clear The diastolic shock often associated with thoracic aneurysm is merely a palpable aortic second sound

(11) *Cardiac Irregularities* Irregularity of the heart was noted in 20 of 61 cases In 10 of the 71 cases the point was not noted In 19 the irregularity was classed as frequent or rare extrasystole and in one, auricular fibrillation This point is worthy of special attention as the number is considerably larger than one would expect in a group of 71 unselected hospital patients

(12) *Abnormal Pulsations* These were noted in 49 of the 71 cases No abnormal pulsations were noted in 12, and in 10 the fact was not recorded

This appears a rather low proportion, but when it is recalled that the series includes a case of transection of the cord, producing paralysis of the bladder, and yet no visible pulsation, it is not so surprising

(13) *Inequality of the Pulse* This has been given much space in textbooks as a sign of aneurysm. In this series it was noted only 9 times and then only in advanced cases. When present other signs of aneurysm usually overshadow it. Unequal pulses are more frequent from other causes, as an anomalous radial artery. As an aid to diagnosis I believe its importance overestimated. However, a weaker pulse which is also a delayed pulse is occasionally a very striking and important sign of aneurysm.

(14) *Blood Pressure in Aneurysm* One is not surprised to find a wide range of blood pressure in aneurysm. There is not a preponderance of cases with hypertension. I have observed an eroding aneurysm on a syphilitic basis with a systolic blood pressure of 180 and diastolic of 120. I think this must be considered a case of hypertension which subsequently developed an aneurysm.

The curves on blood pressure would be more instructive if they could all have been studied in the same stage of advancement. Many of the series are advanced cases, and many are terminal cases and have no blood pressure readings. (See accompanying graphic representations)

If the blood pressure readings are arranged on an average curve it is found that the apex of the systolic curve is reached at 140 and of the

diastolic at 90. This I believe the most common blood pressure reading for aneurysm of the thoracic aorta. Such a blood pressure reading in a syphilitic subject, complaining of pain in the chest and dyspnea, should make one strongly suspect aneurysm.

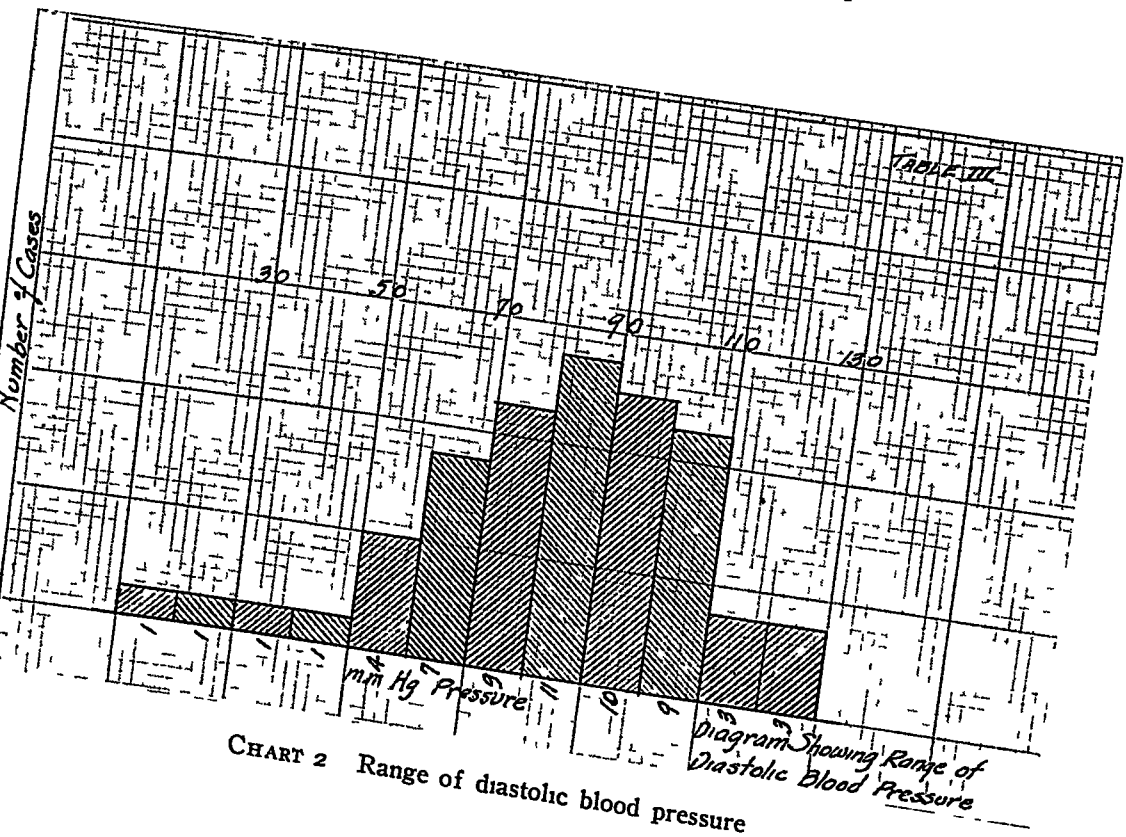
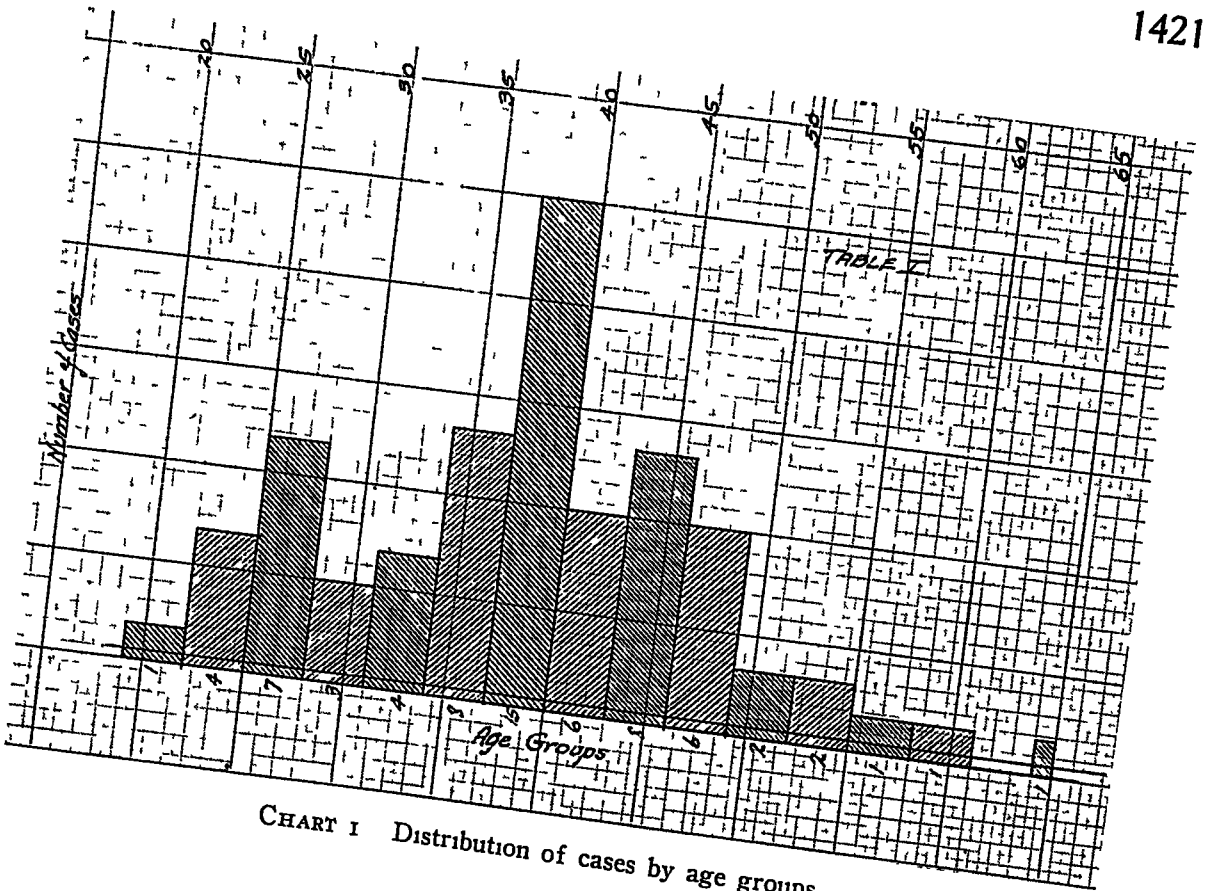
TABLE V  
TABLE OF BLOOD PRESSURE

SYSTOLIC		DIASTOLIC
Above 210	3	140-150 0
170-180	4	130-140 0
160-170	3	120-130 3
150-160	4	110-120 3
140-150	5	100-110 9
130-140	18	90-100 10
120-130	7	80- 90 11
110-120	7	70- 80 9
100-110	8	60- 70 7
90-100	0	50- 60 4
80- 90	2	40- 50 1
70- 80	1	30- 40 1
60- 70	0	20- 30 0
50- 60	1	10- 20 0

(15) *Hoarseness* This occurred in 30, not present in 26 and not mentioned in 15 of the series. It was the first symptom in one case. When present, there are usually more outstanding signs and symptoms. One would hardly be justified in suspecting aneurysm on so common a symptom without supporting evidence.

(16) *Dysphagia* Was present in 14 cases, absent in 47, and not mentioned in 10, and was the presenting symptoms in two cases. While 14 is a relatively small number of the 71, still when present, dysphagia is a very striking symptom and it deserves all the attention given it in literature.

(17) *Tracheal Tug* First observed by Oliver, has been noted in 12 of this series, absent in 47 and not mentioned in 12. It has not been of much help



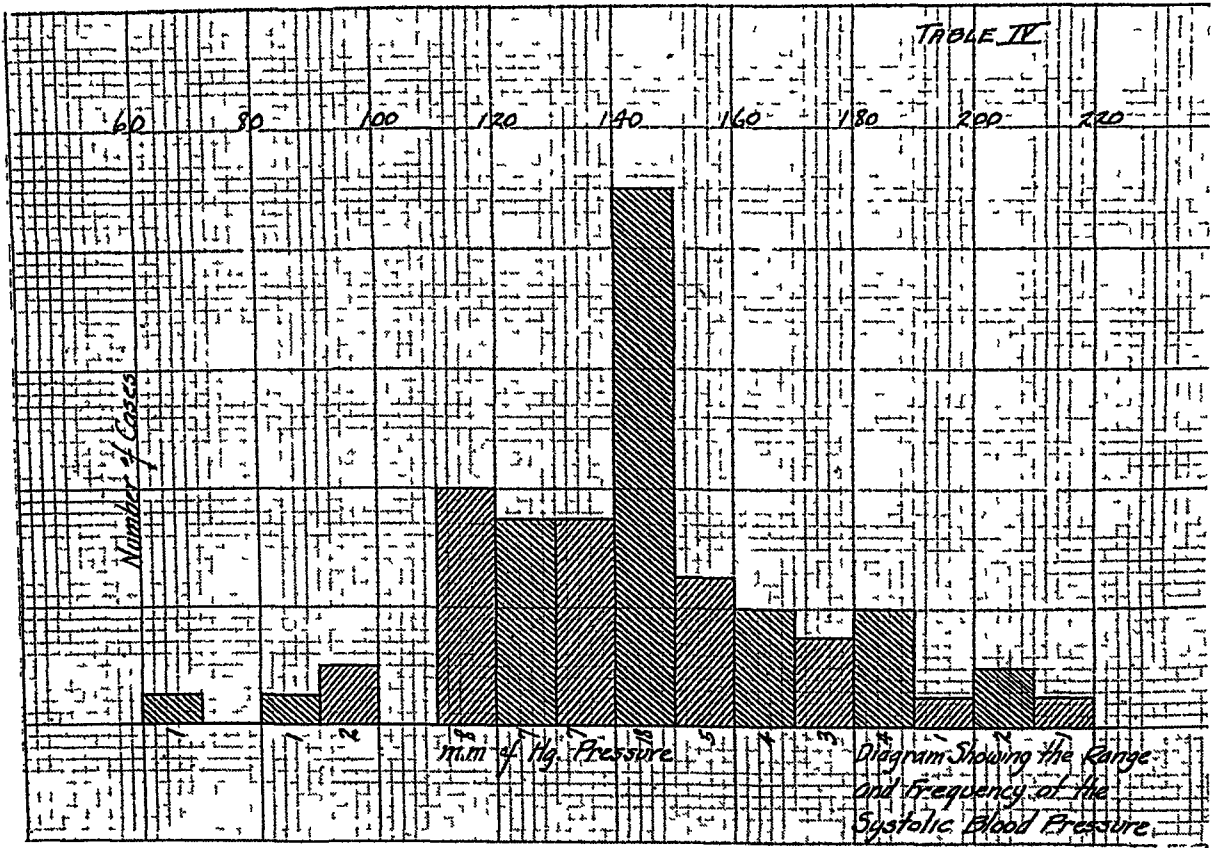


CHART 3 Range of systolic blood pressure

in diagnosis. It is present only in those cases pressing on the trachea and primary bronchi. Other signs usually overshadow it. It is not nearly so important as the accentuated aortic second sound and the character of the blood pressure.

(18) *Hemoptysis* Spitting of blood occurred only 12 times in the course of the disease in our 71 aneurysms. It has never been the presenting symptom nor the immediate cause of death.

(19) *Inequality of the Pupils* This was formerly supposed due to aneurysm, but now generally attributed to cerebrospinal syphilis, old iritis, etc. It has not been of much assistance in diagnosis in this series. There must be a few cases of aneurysm which present a true Horner's syndrome, but they are not of frequent occurrence.

In this series the pupils were normal in 46, abnormal in 13, and not mentioned in 12.

(20) *Glandular Enlargement* A general glandular enlargement was noted in 42 of our series, not present in 11 and not mentioned in 18. It will be seen this compares favorably with the positive Wasserman reactions. It is well known that in some cases of late syphilis, glandular enlargement is no longer present, though this may have been present in the earlier stages. However, one is impressed with the large number of cases of persistent glandular enlargement in this series of aneurysm.

(21) *Cause of Death* This was known in 41 of the series. They are grouped as follows:

Rupture	17	is a corollary of Cabot's observation
Suffocation	9	that the heart is rarely enlarged in un-
Chronic Passive Congestion	7	complicated aneurysm One is im-
Post Operative	3	pressed with the larger number which
Pneumonia	2	died of pressure on the trachea and
Multiple Pulmonary Infarctions	1	consequent suffocation These cases
Cirrhosis of Liver	1	are prone to die earlier than those
Mesenteric Thrombosis	1	which grow expansively and rupture

From this table of causes of death, it is seen that about 42 per cent died of rupture This corresponds with the experience of others who have collected statistics on aneurysm One other fact is worthy of note Only 7 died of congestive heart failure This

(22) *Necropsies* Necropsy was performed on 32 of the 71 cases In the other cases the diagnosis has been quite obvious through physical signs and roentgenographic examination



# Chronic Pulmonary Infections in Childhood\*†

By ALLEN K. KRAUSE, *Tucson, Arizona*

FOR years our withers have been wrung by an unremitting chorus of concern over the sad, yes, the desperate case of the child with tuberculosis. One with a fair memory need not ask for particulars. Most of us here whom age is beginning to beckon set out to practice medicine with the fixed idea that a tuberculous baby must die, a preconception that, to my knowledge, bore fruit in a pediatrician of repute preparing an aspiring and unsuspecting mother for the inevitable by solemnly, yet as gently as possible, informing her that her flourishing young heir of six months, off color for the day, could not survive into childhood—all on the strength of a positive Pirquet test. This eminent physician will soon no doubt be ministering to the children of the baby he years ago condemned to certain and early death, a baby who compassed a healthy childhood and vigorous adolescence, and now knocks at manhood's portals, still Pirquet positive, we suspect, but enviably healthy.

With the dismal dogma of inevitable fatality of infantile tuberculosis went the no less upsetting one of ex-

ceptional susceptibility of the child to the disease and of slim resistance to it when acquired. Our knowledge of tuberculosis in early life has expanded vastly, and sent down more and more sound and solid foundations since monographs and textbooks began to labor the thought and enforce the natural inferences to be derived from it. Today the concept seems to be as firmly entrenched as ever; in support of which supposition we need only point to the fact that for the last few years the plight of the child in this world of tubercle bacilli—a rapidly contracting one, by the way—has been bruited as the chief *casus belli*, the most telling call for action in organized anti-tuberculosis effort.

Few labors in this terrain of fleshly infirmity can be more worthy than the struggle against tuberculosis that has aroused the unselfish aspirations of entire nations of modern times to stamp it out. But, after we have got used to working up our own lather and that of the tender-hearted by fervid appeals to sympathies that stand aghast at accounts, in the name of science, of defenseless childhood, it is disconcerting to work over plain and elementary facts that refuse to fit in with the accepted doctrine. Briefly, there is evidence, and plenty of it, that infancy and childhood are inherently not so

\*From the Desert Sanatorium and Institute of Research, Tucson, Arizona

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powerless against tuberculosis. Moreover, a growing understanding of tuberculosis in early life and, indeed, of tuberculosis at all ages, casts increasing doubt on any idea of unusual or excessive susceptibility to tuberculosis during the formative years. Finally, the chief support of such an idea has come from opinions formed long ago, when our knowledge and comprehension of tuberculosis were relatively quite imperfect.

For instance, the time was not so long ago—it was within the lifetime of many of us, that authorities were disputing the identity of tuberculosis of certain regions with a disease called scrofula, that a few men, well in advance of their day, were timidly suggesting that pulmonary tuberculosis was a not infrequent form of the disease in early life, as others, representing the weight of opinion, made of it an exclusively adult type, that to medicine at large real tuberculosis in infancy and childhood meant meningitis and generalized miliary disease, and that any idea of concealed, or non-active, or obsolescent tuberculosis at these ages simply did not exist.

The results of observations in such a simplified realm of tuberculosis, the inferences drawn, the concepts formed, the doctrines erected, were natural, logical and plain. When a physician's view of the disease was restricted to meningitis and the miliary type, he had, of necessity, to conclude that that disease must terminate fatally, just as would his modern brother today in the same circumstances. But tuberculin testing and bacteriological investigations and X-ray observations give the modern confrère tools that no longer

allow him to so circumscribe his appreciation of tuberculosis. Little by little, yet not so extensively nor so alertly as he ought, he has widened the boundaries of what has come to stand for tuberculosis. The meaning of scrofula has become settled. The lungs of infants and children provide focal soil for tubercle bacilli as frequently as do those of adults, while their lymphatic adnexae emerge as the most common of reservoirs for infection. The skin, the eyes, the ears, the enteric lymphatics add enormously to regions where tuberculous effects may commonly be found. Tuberculosis in the infant and child becomes as far-flung as in the adult, in whom pulmonary involvement is the type of tuberculosis, active, and even more so far-flung, yet not in the sense of generalized miliary disease, with progressive foci everywhere. As we become alive to possibilities, we find child after child with tubercle at several locations—pulmonic hilum, lung, conjunctiva, skin, and perhaps bone or joint thrown in for good measure—yet in constitutional health that is merely indifferent.

We have advanced to a point where we can appreciate how tuberculosis in infants and children is repeating the same experience, as regards our comprehension of it, that it has undergone for every part of the body. Broadly, we can lay it down that the prognosis of tuberculosis anywhere—of any and every part of the body—improves in direct proportion to our ability to recognize it. It was so for the lungs, then for the larynx, and now for the intestines, and who can say that it will not be so for the men-

inges? And the case is no different for infants and children

If, let us say, the diagnosable cases of tuberculosis of the lungs were still restricted to those that would yield to Laennec's methods of detection, it is doubtful whether our vaunted superior modes of treatment would save many more patients than were rescued by Laennec and his followers. For, to Laennec the "case" of pulmonary tuberculosis began at a stage now regarded as far advanced and, in general, hopeless. But the century following Laennec saw the boundaries of this clinical condition pushed to an extent that they not only embraced types of tuberculous infections that would heal themselves, but even promised to include, and actually did include, types that would likely never set up a condition that required treatment. Similarly, the outlook for tuberculous enteritis has lately improved enormously, as by refined roentgenology we manifold our cases, and so take credit for curing a large proportion, which, not much longer than ten years ago, were healing themselves as they passed unnoticed.

In like manner we have widened the field of tuberculosis in childhood. Proceeding naturally from the more apparent to the more concealed, we have added condition after condition of tuberculous infection, to indicate the existence in early years of ever more benign states—types—of the infection. We have now gone far enough to be able to say that, by and large, tuberculosis, as such, is essentially a non-progressive infection in not only the adult, but in the child also, and, un-

less all signs fail, in the infant likewise—if not no less.

By this we mean to set down our belief that, if the truth as to incidence of tuberculous infection were known, we should find that, though actual proportions might differ, all periods of human life would exhibit a great preponderance of benign, that is, non-progressive, non-clinical, non-active tuberculous infections over progressive, clinical, active ones. Indeed, after one has tried to account for the several variables of environment, as these are known and presumed to influence tuberculous infection and its results, and as they may operate differently at the different periods of life, one will likely find little to support a thesis to postulate a greater innate defenselessness toward tuberculosis during human life's tender years.

As for the period of childhood, all signs point to a condition of extraordinarily high resistance. Childhood is really mankind's "golden age" as regards tuberculosis. Enlarging spheres of activity and experience multiply contacts for the infant emerging into childhood and the child on its way to adolescence, whence, ever-increasing opportunities for infection, numerically if not quantitatively. Yet the results are not what would be expected, and they could hardly be predicted.

First, the mortality from tuberculosis falls sharply from that maintained in infancy, and soon reaches a nadir that is maintained until late childhood, when the rise to the mortality peak of manhood begins. Never before and never again afterward do we find such low tuberculosis death rates as obtain in childhood, and this too is the period

when opportunities for infection are most common and infections are being received most frequently. If it were a period of peculiar freedom from disease and respiratory disorders and ill health in general we might grasp at the circumstance to explain the paradox of declining mortality with mounting infection. But childhood is not such a period. It is the very reverse, and is withal that time of life when any consciousness as to personal cleanliness and bodily care is at its lowest and when these needs are least looked after.

Again, the morbid effects of the tubercle bacillus in the child are ordinarily of a kind to suggest unusual tolerance for the bacillus. Tubercles and other eruptions of tuberculous origin bespeak a dissemination of bacilli throughout the body; they are a frequent occurrence in children with health but slightly if at all impaired. The same thing may be said for phlyctenular conjunctivitis and keratitis, especially when combined with tracheo-bronchial lymphatic and perhaps cervical lymphatic involvement, associated too with the perennial Ghon focus. The bacillus has made the rounds of the body, has focalized appreciably at several remote points and presumably at numerous other points, yet the child is so slightly affected that in the circumstances only too many physicians centre all attention on tonsils and adenoids. One's amazement grows with one's experience with what in the way of tuberculosis the child will often tolerate in the lungs, and maintain fair health throughout. The bone and joint foci that remain localized and are recovered from far exceed those that

break through and spread to a fatal termination. The abdominal lymphadenitides and the peritonitides that heal again outnumber those that erupt to generalized miliary disease and meningitis. Indeed, grade for grade, matching focus with focus and locus with locus, it is questionable whether the adult will compete with the child against the onslaughts of tuberculosis. My own opinion is that the child "has the edge." When we get down to examining more ailing children for pulmonary tuberculosis, and diagnosing more of them with the slight changes that are sending adults to the sanatoria, we shall know more about all this. At this juncture I would merely make a passing plea for a general recrudescence of tuberculin testing in pediatric practice. I imagine, too, that a cardinal rule of diagnosis in internal medicine can be no less fruitfully applicable for children to wit, that the more obscure an ailment, with earmarks of an infection, remains, as one after another diagnostic test falls short, the closer one is approaching to a diagnosis of tuberculosis. And it is here that tuberculin's evidence grows most compelling; for a positive test gains in meaning as other possibilities dwindle.

I am not taking this attitude toward tuberculosis in children with the intention of belittling its gravity. I do so mainly to drive home the point that in early life tuberculosis may, and perhaps the more frequently does exist, in its benigner forms, that the physician should be alive to this common occurrence, that he should divest himself of any idea that tuberculosis is an impossible diagnosis unless he is con-

fronted by serious physical manifestations; and that, if the truth were known, the more common clinical presentation of tuberculosis in early life appears to the physician as the hardly sick child, or the lackadaisical child, or the transitorily upset child, or merely the overirritable child. Tuberculosis in children can have its unmistakable syndrome just as it can have in adults, but, again as in adults, it can throw out its warnings in the most unexpected and most equivocal of guises, and a resistant soil in childhood can yield a no less abortive and stunted harvest of physical changes.

Again, as in adults, tuberculosis in children at any time may or may not be arousing physiological (functional) disturbance. If, when, and as long as it is deranging function, it must be regarded as clinically active, that is, worthy of medical attention and treatment, and, conversely, it passes outside the concern of medical practice if, when and as long as it does not and promises not to affect the bodily economy adversely.

Personally, I can comprehend no middle ground between tuberculosis active and tuberculosis inactive, as a matter of practical medical concern and as based on a concept of a demonstrable influence of existing tubercle on local or bodily (constitutional) function. At any time foci of tubercle are exerting a telling, an appreciable, influence on function, or they are not so operating. If they are, they are clinically active; if they are not, they are clinically inactive. The term "latent" has latterly come into vogue, but just what it is to express or imply has never been made clear. It obviously

does not essay to take over the well-understood connotations of inactive tuberculosis; it evidently shrinks from embracing attributes that we are wont to associate with activity. It seems in an indefinite way to define a state of tuberculosis that lies or wanders between activity and inactivity. But, is there any such *status quo*, changing perhaps, of tuberculous effect? And, if there is, would its formulation serve a useful practical purpose?

I have had it explained to me that "latent" tuberculosis defines and marks out that condition of tuberculosis in children that is likely to be missed by the average practising physician. But this can hardly be possible, for in actual existence it could have no fixed position in structure, in function, in methodology, or in the profession. I have myself got the impression that there was first created a particular symptomatology, with perhaps fever the crucial element, that was to stand for active tuberculosis, and that then any evidence of the stirrings of tuberculosis that fell short of this symptomatology, especially as the latter lacked fever, were to be denominated as "latent" tuberculosis. For instance, an underweight child, with certain tell-tale markings within the chest yet without fever and, let us say, also cough, was to be regarded as laboring with "latent" tuberculosis.

This would delight the users of the old term "pretuberculosis," especially if such a child came down later with tuberculosis full-blown and with classical signals unfurled. But, could anything be more misleading or more disserviceable in lulling the rank and

file of physicians into a false sense of their responsibility in the premises?

Let us imagine that undernutrition and only undernutrition in a child brings the latter to a physician's attention, and, moreover, that exhaustive examination discloses nothing to account for the inability to attain or maintain normal weight except a focus of tubercle. The next step is to prove that the focus is responsible for the bodily disturbance. If, now, this can be established, how can we regard the focus in any way other than that it is active? If tubercle so affects the body as to stunt it, or disturb nutrition, or set nerves over-irritable and a-jangle, or lower muscular or vascular tone, is not such an influence just as surely an evidence of deleterious effect as is the much more superficial one of disturbance of temperature? Should we not regard the disturbances mentioned as the deeper-seated by far, and therefore as surely the manifestations of "activity" as is a derangement of temperature, which is really rather incidental?

There is indeed no royal road to the diagnosis of tuberculosis, and in medical practice an expanding knowledge has made "tuberculosis" synonymous with "active tuberculosis." And the first step in the approach to this diagnosis is a grasp of the general principle that nowadays three particulars are always necessary to the conclusion. These are, first, that there is something awry, as signalized in a region, an organ, a body out of rhythm, let us say; second, that within the same organism lies specific tubercle disclosed, and, third, and most important, that the arrhythmia, the disharmony, the derange-

ment, can be brought into correlation with the tuberculous formation. Given these, and almost all aberrations of the flesh will take almost equal rank as harbingers of tuberculosis—of that tuberculosis that merits, that demands medical attention—of, if you please, active tuberculosis. Unwonted pallor will rank with cough, premature systoles, depressed blood-pressure, over-irritable heart with elevation of temperature, nervous over-irritability with undernutrition, and, usually, if not always, there will show through the cardinal symptom of tuberculosis—asthenia—loss of tone—whether of skeletal musculature, of vascular tree, of psyche, of special senses, or of digestive tract. With the presence of tubercle proved, any aberration that can be tied to it spells tubercle in only one form—"active tuberculosis." In the presence of tubercle a completely sound body, functionally speaking, guarantees inactive tuberculosis for as long as no derangement of the bodily economy rears its head. There is no middle ground—no "twilight zone" of pre-tuberculosis, of latency, of preparation or maturation or concoction, in a clinical sense, much as anatomical, structural shifts may be afoot—changes under way within tuberculous foci, to at last reach a quantity or quality that stamps telling noxious effects upon the animal organism. The only reservation that could hedge this dogmatic generalization would have to account for the more or less permanent functional derangements set up by the residua, the healed remnants, of healed or competently invested tubercle of the past.

For the rank and file of physicians tuberculosis has far too much usurped

the field of attention to chronic pulmonary infections. They are still accustomed to give all too scant thought to the possibilities of other than tuberculous *focal* infections within the lungs of infants and children. Yet, in early life such focal changes of non-tuberculous origin and nature are anything but rare, they are damaging, even in their minor phases they can be a tremendous drag on the child's normal development; they frequently set the stage for a later life of inefficiency and invalidism. They create a situation that should be grasped better by the generality of the profession.

Bronchiectasis, when fully expressed, is so definite a condition, it has so characteristic a symptomatology, it has originated out of so stereotyped a set of conditions, it is withal pregnant with so serious an outlook for the child, that its almost complete recognition would seem to be assured and expected that is, when, as just said, it is fully expressed. However, in medical practice one gets the impression that the natural history of bronchiectasis is quite otherwise. The percentage of correct diagnoses attending the adult bronchiectatic patient's first resort to medical advice must be amazingly low, and the disease ranks high as one commonly detected first by the consultant and specialist. With experience one's astonishment grows at the numerous patients rounding out their years at tuberculosis resorts and even in sanatoria, and being treated for pulmonary tuberculosis, all the while they display such prime features of non-tuberculosis as negative (for acid-fast) sputum, involvement restricted to lower

lung, and disproportionately minor constitutional versus obtrusive local symptoms. Surely a few weeks should suffice to rule out tuberculosis in most of these cases, and again and again this time will be shortened by tuberculin skin tests that result negatively—if only the tests are done.

Sometimes these cases will turn out to be abscess; sometimes that nondescript condition that masquerades in text-books as "chronic interstitial pneumonia," if indeed there be any such pathological reality; but most often, I suspect, they express clinically the local and constitutional effects of damaged air-passages, expanded permanently and dilated at certain points, and scarred and exuding secretions that cannot find prompt or adequate evacuation. A muco-purulent sputum, of whatever amount, that fails to yield acid-fast bacilli on repeated daily examinations and that emanates from a patient without evidences of diffuse bronchial involvement but with signs of focal changes below mid-lung, should without undue delay send the physician to at least imaginings anent the presence of bronchiectasis. In most instances these imaginings need not be vague, nor will they be vain, they will be translated into reality.

I would disclaim all pretensions to an unusual or extensive experience with bronchiectasis. Yet it is just because my contact with it has not been exceptional that I am the more impressed by the stretch of time that is wont to elapse between the patient's onset of illness and his at last correct diagnosis of bronchiectasis. So often has this happened that I have long taught that for the adult the average interval

is to be measured in years. Proportionately, for children the case is no better. If anything, it is worse, which makes it all the more regrettable; for if ever there was a disease whose potentialities required its early diagnosis, that disease is bronchiectasis. It may not kill as surely as tuberculosis, nor as quick. It may not bring the patient low as soon and as often, indeed, an antithetical disproportion between local and constitutional symptoms is a feature that we have stressed as among the distinguishing marks of bronchiectasis and tuberculosis. But, grade for grade, and short of the bed-ridden stages, bronchiectasis can be (and is) far more disabling than tuberculosis, and only too often far more impeding and offensive as well, while as to permanent healing or relief from symptoms, there is no comparison—the curability and amelioration of tuberculosis at advanced stages are vastly ahead of those of bronchiectasis in its earlier phases.

Short of confirmed bronchiectasis, yet on the way to it, there must be an almost illimitable gradation of minor pulmonary changes of greater or less permanence. Established bronchiectasis is wont to challenge our therapeutic resources, and tax these to the utmost, and the average result of treatment of even its milder phases is but indifferent success. For this reason alone it is important to detect the disease early, and make every effort to stay its progress, but even then a wisdom born of experience makes us chary of promising too much. Here indeed is a situation that points to the great importance of recognizing in the lungs of children all focal changes of

infectious nature—spots of permanently damaged tissue, with potentialities for progression and for indefinite and prolonged residence of microorganisms—patches that may go on to bronchiectasis, not to mention abscess, or may, now and again, flare into acute bronchopneumonia. That the lungs of children are very frequently the abiding places of unnoticed and unsuspected non-tuberculous foci of infection we are convinced. That the fact should be more generally appreciated and acted upon in the circumstances we are no less certain. It would seem that much ill health in childhood that now passes for disturbances in the upper respiratory tract,—the nose, the throat, the ears, the tonsils, the sinuses—is actually and largely the expression of chronic intrapulmonary infection, and that, moreover, not a little of the bronchopneumonia of childhood occurs really as a rather incidental acute event, punctuating the much more prolonged course of a preexistent chronic infectious process, and not as the primary incident that ushers in the chronic changes that we detect later.

We have come to believe that the guise taken by these chronic focal infections in children can be no less misleading and impenetrable than those assumed by tuberculosis. But, masking them most frequently perhaps is all that goes into what we call “oversusceptibility to catching cold,” as common a complaint as brings the child to the physician.

Now, oversusceptibility to colds can be of every degree and duration. It can be the habit of years or the unexpected manifestation of a first winter—a series of nothing more disturbing



than recurrent snuffles and running nose, or a succession of repeated febrile attacks with bronchitic symptoms uppermost. It may yield readily to judicious attention to faults in the nasopharynx or tonsils, or to correction of improper habits and parental care. On the other hand, it may resist the most expert measures and regimens designed to curb it. After everything corrective and curative is done, there remains a discouraging number of children whose health is variably and materially impaired because of oversusceptibility to colds and its consequences. At least, this is the outstanding complaint as voiced by the parent who presents the child to the doctor.

Whether the child is just emerging from infancy, or is six, eight or a dozen years old, there is an almost stereotyped sameness to its story—its clinical history. Its trouble all started with a hard common cold, an attack of so-called "grippe" or "influenza," or one of the acute infections of childhood—whooping-cough ranks peculiarly high here, with measles also prominent. This happened several years ago, since when the child has never been the same as before. It has shown an increasing tendency to contract fresh colds. These begin with the first change of season to cooler weather, and have latterly been recurring to such an extent as to house the child for much of the winter and interfere seriously with schooling. Seizures of bronchitis, with fever, are becoming more severe and more prolonged, and between acute periods a chronic condition of cough has settled in. These repeated illnesses have begun to tell

on the child's general health, as shown by noticeable pallor and a falling off in tone, vigor and nutrition. Because of occasional symptoms pointing to ears or throat, these, with perhaps the sinuses have been looked into, and adenoids have been removed and a paracentesis of the ear performed once or twice for an intercurrent otitis media. But what is giving the parents most concern are at last undeniable evidences that normal physical development is suffering, and the idea that a now confirmed pallor, undernutrition and listlessness mark a declining resistance to the normal shocks and stresses of childhood that will eventuate in fresh colds. Efforts to protect the child against exposure almost invariably result in over-coddling, and thus the vicious circle is fortified.

Up to this point most children of this type will have not gone beyond the care of the general practitioner, the family physician, except for special work that may have been done by the otolaryngologist. They form a rather unsatisfactory part of the former's practice, as year succeeds year with slight if any improvement, and adolescence is hopefully awaited as a time for the child to outgrow its "delicate constitution," and with this its genius for catching colds. It is only when, as frequently happens, an overly hard "cold" strikes in, with now plain evidence that the lungs themselves are affected, that a real turn in events sets in.

The child falls ill with symptoms and signs that are unmistakably those of bronchopneumonia, which send the physician to more assiduous attention to the chest. The involved spot, ex-

tending out and downward perhaps from the root, is determined, and, as the child recovers from the acute illness, this spot is found not to clear completely. Râles fade out only gradually, and not entirely until long after clinical recovery from the pneumonic attack; while, still more significant, X-ray changes in the involved territory persist long after the last pneumonic râle has disappeared. The child, meanwhile, has resumed its old habit of "delicate constitution" with chronic cough. To the attending physician its attack of pneumonia has made one important difference; in his opinion, this has left a remnant of unresolved tissue in the child's lung, a patch that bids fair to undergo fibrotic transformation. The course of events has been plain: the child's susceptibility to colds had at last laid him open to pneumonia, a first manifestation of pulmonary involvement, which, in its turn, has put its rather lasting mark upon the lung. Whatever of moment may happen to the child later will have had its origin in the permanent damage done by the pneumonia. This will date the real beginning of any progressive pulmonary process that the years to come may bring forth: that is, all this is as the physician sees it.

We have come to doubt so orthodox an explanation. When good fortune has presented the necessary positive evidence in a few cases of the type under discussion, this has been of a kind to show unerringly that, prior to the pneumonia and probably for years, there had been in existence an undetected patch of focal change, non-tuberculous in nature, in the child's lung. Roentgenography, done months

before the acute pneumonic phase, had made sure of this datum. Then, most important to an understanding of cases of this type, when the acute bronchopneumonia did supervene, it involved the lung in the identical territory that had long been under observation as manifestly diseased.

That is to say, during the more ordinary period of the child's general complaint of oversusceptibility to colds and for some time preceding its clinical bronchopneumonia, there had been under medical observation a region of abnormally increased density and exaggerated markings that extended from the pulmonic hilum outward and downward into the lung—a type of change that had been regarded as definitely pathological and had aroused suspicions of incipient bronchiectasis yet could not be substantiated as such, that is, as a process that had progressed that far. When now the bronchopneumonia appeared, this was localized in and to the region in question. Roentgenographically the observer beheld the picture of a preexisting focus of morbid change that had, as it were, slopped over into the immediate neighborhood; as, under the spur of acute exacerbation, it poured forth those elements that converted, for the time being, the immediate region into a pneumonic patch. An abnormal, shadowed density, already and ostensibly long in being, was extending its boundaries out into the surrounding pulmonic field, as it too was undergoing certain changes in quality. It was plain that the pneumonia was originating in an already present focus of diseased tissue.

When now, as happened in the usual time, the pneumonia cleared, there took place simply a retreat, a drawing in of the pathological shadow to approximately its old contour; until, after some weeks, it looked hardly different in size and "texture" from the density observed months previously, before the attack of pneumonia. The point made above was that ordinarily in practice such a patch would be regarded as having originated from an unresolved pneumonia, whereas, the truth is that the pneumonia but represented an acute incident occurring in the course of an essentially chronic focal process, an acute exacerbation of a more permanent non-tuberculous focal infection that at all points differed little from analogous episodes that so normally punctuate the course of chronic tuberculosis.

A growing experience has led us to believe that cases of this type are anything but rare, that, indeed, there is a condition of focal non-tuberculous infection in childhood that in frequency and gravity will rank with the better appreciated tuberculous infection and which, in essential features, bears many striking resemblances to the latter; moreover, that perhaps the most common approach to medical attention for these non-tuberculous focal infections will be through the complaint of unusual susceptibility to colds. It is indeed this prime feature that forms the main burden of my present thesis.

I have recently had brought to my attention a case, the son of a physician, with a history of three recurrent attacks of bronchopneumonia, and also the story of oversusceptibility to colds that antedated the first pneumonia.

Fortunately, this boy's chest has been X-rayed at intervals since before his first acute upset. In all particulars his case repeats what was sketched in outline above from the time of the first X-ray films there has been in existence an abnormal basal density, and every exacerbation of pneumonia has had its origin and its being in this territory. And now, to fill in these more or less ideal and composite descriptions with more concrete particulars, another actual case may be summarized briefly.

It concerned a youngster, five and a half years old, born into and bred in a home of wealth, comfort and intelligence, and exceptionally healthy and flourishing from birth until ten months old, when severe whooping-cough, to which the beginning of all present trouble is attributed. Since the whooping-cough every autumn and winter have brought a succession of fresh colds that have increased in severity and duration, with asthmatic features appearing first about a year ago. From age one to four years, summer, with its warmer weather, would gradually rid the child of cough and ensure it several months of freedom from acute seizures of cold. Increasingly the perennial series of winter attacks have worn the child down constitutionally, but with settled warm weather would come a prompt rebound, and through the summers the child would pick up ground lost in winter. Latterly, however, since four years of age the child has been having severe acute colds also in summer, but these are attributed by the grandmother, who would coddle the child, to overexposure brought on by swimming allowed

by the mother who had been trying to harden him.

At all times the boy has had the most approved medical attention at the hands of physicians of prominence. They have seen to it that the upper respiratory tract and its appendages have been cared for and all faults corrected. About a year ago otitis media, in severe form, appeared for the first time. This recurred, but has given no trouble since the spring of 1929. At about this time also asthmatoïd symptoms began to feature the case. There has been nothing to suggest a real or classical asthma, and any evidences of hypersensitiveness have been conspicuous by their absence. There has, again, been never any attack of typical bronchial asthma. What passes for "asthma" are attacks of wheezing, crowing and coughing, not particularly severe nor embarrassing to respiration, which are wont to come on unexpectedly. If the child is sensitive to anything it is to exposure to cold—to draughts of cold air or to stepping with bare feet on a cold floor. Such exposure will often lead immediately to coughing and wheezing. Ordinarily, the chest is clear on physical examination, and by this method alone the examining physician would pass up the child's chest as normal. Let the child step on a cold floor, and he soon begins to cough and wheeze, and now râles appear, especially in the back, to the right and at about the angle of the scapula. Ordinarily, too, he has a teasing non-productive cough that comes and goes irregularly. Seizures of apparently fresh colds, which last a few days and during which râles may or may not appear transiently in

the area mentioned, are frequent. The child's whole regimen at home has been designed to prevent these acute colds, and has resulted in a habit of life that is softening, and is, if anything, laying the boy more open to exposure.

The first suggestions of asthma sent the physician to more exhaustive search for pulmonary trouble, and in June, 1929, X-rays of the chest were taken, for the first time. The search was successful. Extending out into the lung from the right hilum, in the location where râles were to be heard on occasion, was a fairly extensive opacity that was distinctly abnormal. This naturally suggested tuberculin skin testing, which resulted negatively. Accordingly, the condition was regarded as a non-tuberculous focus of infection and its exact pathological structure undetermined.

Since the child was in apparently normal constitutional health, he was allowed and encouraged to lead an active outdoor life during the early summer of 1929. In August he fell acutely ill with pulmonary and general symptoms that were immeasurably more severe than ever before. This was the onset of a serious attack of bronchopneumonia that lasted several weeks. During this illness the usual pulmonic physical signs of bronchopneumonia were confined to the right base, and X-ray disclosed a marked extension of the density noted on the earlier film. To repeat the characterization used above, the infectious focus first noticed in June seemed to have "slopped over." At any rate, there could be no doubt that here had taken place an acute exacerbation of a more

chronic sluggish process The sequence of events was precisely that which a chronic focus of tuberculosis is accustomed to undergo, nor, during the next few weeks, did the course of the disease differ essentially from what one again and again sees in tuberculosis

The symptoms of pneumonia subsided in good time, and with them the signs; and coincidentally also the abnormal shadow in the lung shrank to almost its former proportions Perhaps it was a little larger than before, but within two or three weeks it was back to approximately the same size and appearance it had shown in June

A month after recovery from pneumonia the boy arrived at the Desert Sanatorium, to enter upon treatment that was based primarily upon a climatic environment in winter that would reduce to a minimum the chances of catching fresh colds and thus flaring his chronic pulmonary process Upon arrival he was *r*âle-free, and remained so except for occasional days on which there was always an access of cough and sometimes of wheezing However, the child went through the winter in Southern Arizona without a seizure that could really be called a fresh cold. Except for occasional days he continued *r*âle-free, as meanwhile but little roentgenographic change appeared in his lung

Several other patients observed during the same period have had essentially identical histories Whatever differences stood out were merely those of detail One or two cases had lacked the sharp and definite onset, as signalized by whooping-cough or pneumon-

ia ushering in a later childhood of "delicate constitution" and tendency to catching colds. Careful questioning of intelligent and cooperative parents made sure of this, as there emerged the story that, at one age or another during the first few years of life, a previously robust child had contracted a cold, after which a growing tendency to fresh seizures at last created a situation of settled cough, with acute exacerbations and noticeably impaired general health, always worse in the cold season and abating in summer While all our children showed definite pulmonary change, always basal, roentgenographically its extent varied from minimal to marked In none of this particular type were the X-ray features, symptomatology and accessory findings (for instance, finger-tips) of a kind to warrant the diagnosis of clinical bronchiectasis Not all children had had diagnosed acute exacerbations of bronchopneumonia, and in several the probabilities of their having had it were slight

Without exception these patients had had some special work done on nasopharynx, tonsils and adenoids, sinuses or ears, which rarely showed active trouble while under our observation If it be assumed that these patients' oversusceptibility to colds depended on faults in the upper respiratory tract (and *adnexae*), our own patients of the type in question gradually engendered the idea that, while this may have been true originally, the cases had long passed the stage where the upper air-passages were responsible alone At some time or other the lungs had also become affected, and rather permanently so, and it was question-

able whether at present anything but the pulmonary focus was contributing to the child's apparent defenselessness to the common cold. Indeed, little by little there developed the idea, as hazarded above, that in a great many children an abnormal tendency to the common cold is but a leading clinical expression of the presence of a non-tuberculous pulmonary focus. Perhaps the latter had originally developed in association with trouble in the upper respiratory tract. But, once created, it had become a permanent affair, and remained after upper-respiratory disturbance was allayed, and thus kept up the original complaint.

We have long learned in tuberculosis how foci of the infection, residing permanently in the lung, can be (and are) of every conceivable grade of extent and content, and therefore of clinical significance. Indeed, we have learned our lesson so well, that we teach that the presence of tubercle in the body comprehends not only foci of many kinds and sizes that are appreciable by our various modes of detection, but also a goodly array of foci that are beyond our range of observation. This fact is so easily proved as to constitute one of the important truths of tuberculosis. In other words, a complete understanding of the habits of the infection, tuberculosis, must always postulate that for every focus of demonstrable tubercle there likewise exists an unknown ratio of hidden tubercles, which, for one reason and another, do not disturb function or stand out morphologically sufficiently to make their presence noticeable.

Can the case be similar with these non-tuberculous infectious foci that we have been discussing? We cannot answer with the positive evidence from experience with the child, but we may cite a bit or two of testimony that points to the high probability of the case in question.

For instance, how are we to explain what can be found to happen not rarely in adults, and quite likely also in children, had we the proper opportunities to follow them medically? Instances, such as I am about to enlarge upon, are peculiarly the opportunities of the family physician to whom it is given to observe under many circumstances the same individual patient through the years.

The opportunity will begin, let us say, with a severe common cold. The patient takes to bed with the usual symptoms, including a fever of a few degrees, and the examining physician detects basal râles. Within three or four days the patient makes an ordinary recovery, as the temperature falls to normal, and he prepares to get up and be about his daily work, feeling a little bit shaky perhaps, yet as well as can reasonably be expected immediately after a hard cold. But now the physician is disturbed to find that, though clinical symptoms are about over with, the base still shows râles. Justly concerned, he counsels the patient's remaining in bed. Fearful of pneumonia, he plans to keep the patient there until the râles have disappeared.

By the end of another week we have a patient who is feeling better every day and impatient to be up and about his daily round, yet displaying a lo-

calized patch of râles that is hardly less noticeable than during his acute illness. There may be a little cough, and perhaps scanty expectoration, but otherwise the patient is thoroughly asymptomatic, and to all intents and purposes he has recovered completely. Only by virtue of the râles can he be regarded as ill and still requiring fairly rigorous treatment.

Patients of this type present a pretty problem to the responsible physician who attends them for the first time. If he decides to "wait out" the râles before allowing the patient up, he may wait for months, especially if it is winter. Frequently such râles do not disappear promptly. Indeed, they do not fade out completely for months. In not a few patients they will persist until the warm and settled weather of summer, when gradually they die away. Call this condition what you will—pneumonitis, subacute or subchronic, or with delayed resolution, or minimal pneumonia of kindred types, or localized bronchitis—we really don't know a thing about its pathological nature, its structure.

But it is the patient who, as it happens, begins to repeat this experience, that becomes the really interesting subject for speculation. It may be the next winter, it may not be until several years later, that the physician is called to attend the same patient with another hard cold. There is the same lot of symptoms, with fever again uppermost for two or three days, after which ensues the same prompt clinical recovery as before. Again, too, there are basal râles, which once more do not subside with the other features of the infection. It is not particularly

noteworthy that a patient has contracted a second common cold, for this is the archetype among the habitually recurring infections of mankind. But what is likely to bid the physician pause and reflect is the circumstance that he again finds râles, and again persistent râles, in the very same spot that yielded them before and which, to his knowledge, had been entirely quiet during the intervening year or two. This surely is curious that two separate attacks of the common cold picked up afresh from the outside at an interval of several years, should focalize in the same sound lungs at the same place.

The case becomes still more curious when, as occasionally happens, a patient will go through this performance, not once or twice, but repeatedly through the years: when every recurrent acute cold will make for focal râles located always in the same region, which, in the intervals between attacks, will be found to be not only râle-free but also normal to ordinary methods of physical examination.

Nevertheless, it is possible that, the more frequently this experience is repeated in the individual patient, the less curious it becomes and the more certainly we are approaching a satisfactory explanation. Every recurring episode of this kind enlarges the probability that these patients have actually a permanent infectious focus within their lung, minimal perhaps and undetectable in ordinary normal times by the methods used, yet, like foci of tubercle again, capable of exacerbation under the influence of intercurrent infection (for instance, the common cold), when now they suddenly

flare to proportions recognizable by our methods of diagnosis

A recent patient furnishes a beautiful example of perhaps a later phase of this condition. Fifty-three years old now, he began at thirty-seven with a severe cold to enter upon a series of recurring colds and, later, attacks of bronchopneumonia that succeeded one another, always in winter through the years between. Always were the changes focal and localized in the same place, the left base. After some years the changes were of a grade and kind that shadowed the X-ray film, and during the past few years, that have been featured by several pneumonic seizures, the morbid markings on the films have extended. Latterly an excavation (abscess) has come into view in the centre of the affected territory. For some years there have been increasing asthmatoïd symptoms, whose onset was not until years after the beginning of the pulmonary process and which respond with notable delicacy to exposure to cold. Almost twenty years of repeated reactivations of this non-tuberculous focus have left their mark upon his heart, which for the first time displayed serious embarrassment last winter during the most severe attack of bronchopneumonia yet experienced. The case is an almost perfect example of the slow yet orderly march of a non-tuberculous focus from small and merely symptomatic beginnings to extensive pathological change. We have here a march that at present we may be allowed to imagine something as follows. With or without morbid changes in the upper respiratory tract, microorganisms other than tubercle bacilli gain access to the lungs, take

hold, and focalize, preponderantly out from the hilum and below midlung. Tissue changes may be so minimal as to escape detection and recognition by any present diagnostic method. It is conceivable that ordinary autopsy would miss them, as, too, would histological examination short of complete serial sectioning. Like the gonococcus in the prostate or the posterior urethra, the *Bacillus typhosus* in the gall-bladder, the *Bacillus diphtheriae* in the tonsil, the *Bacillus tuberculosis* anywhere, the germs can live on indefinitely, embedded in minimal focal lesions, and multiplying sparsely. Like the focus of tuberculosis, this non-tuberculous focus is capable of indefinite activation, especially by other intercurrent respiratory infections. In its lowest clinical phases it throws out clinical symptoms and signs only when thus activated, and its earliest detectable phases are these periods of audible focal râles, noticeable during activation and often long afterward, and at a stage too poorly developed anatomically to show pathologically on X-ray. At this time and during periods of focal quiescence, the lung will appear normal on physical examination.

Because symptomatology that suggests an oversusceptibility to colds is a prominent feature of cases with demonstrable non-tuberculous focal infection, a marked tendency to colds in children, especially if not satisfactorily accounted for, should indicate a most exhaustive search for pulmonic focal infection. In the absence of all other signs, râles recurring in the same place are first-class evidence of its presence. Because of the incurability of later phases it is important to institute treat-



ment at this earliest presumptive indication of its presence

With a later and more definite pathological development the tissue changes set up by these focal infections begin to cast abnormal markings on the X-ray film. It may take years to reach this stage, though in many children the time is much shorter. What is important is to appreciate that, for purposes of treatment, this is a comparatively advanced stage and that the ideal is to anticipate it with treatment. The chances for acute episodes of bronchopneumonia are now multiplied—attacks which, in their turn, enhance the progressiveness of the focus. This is the stage that will be found in many children whose leading complaint is oversusceptibility to colds, and every effort should be made to detect it in the circumstances. It is also a stage that is often featured by symptoms that suggest asthma, though the symptoms are likely to lack the leading features of those of the classical disease.

Firmly entrenched, these focal infections can progress to bronchiectasis and to abscess, as, too, the tendency to

recurrent bronchopneumonia may become more marked, and that to contracting fresh colds enhanced, and the child shows more decided constitutional effects. At this stage the interminable succession of alleged fresh colds is more likely to be the more frequent acute manifestations of the chronic focus, now more or less active clinically all the time. Attempts to eradicate such foci will be rarely successful. Treatment may palliate, it can hardly obliterate.

In view of our present therapeutic resources (or lack of them) the guiding principle of treatment of the minimal processes will be that regimen in that environment that reduces to a minimum the chances of catching fresh colds or of acutely exacerbating the focus. The standard winter climate is the dangerous element for these patients. They do badly, and repeated activations wipe out all possibilities of healing. At present there is reason to believe that, if taken in hand early enough and if allowed long enough periods of quiescence, many of these foci may attain permanent arrest and healing.

# The Effect of Sodium Malate Combinations Upon Gastric Acidity

By JOHN C KRANTZ, JR, Ph D AND A A SILVER, M D, *with the technical assistance of* BERNARD J. HOFFMAN, *Baltimore, Md*

IN a previous communication to this journal, one of us (J K) (1) studied the metabolism of a certain sodium malate mixture when employed as a dietary substitute for sodium chloride. The mixture studied consisted of 85.5 per cent of disodium malate, 9 per cent of trisodium citrate, 5 per cent of triammonium citrate and 0.5 per cent of manganese bromide. In this work the administration of this mixture of salts in the form of a condiment was shown to influence the acid-base equilibrium of the urine in the direction of the alkaline side. The malic acid was apparently completely metabolized.

A physician friend of one of us (J K) whose stomach acidity was abnormally high and who suffered with the usual symptoms was brought to the attention of the authors. It was suggested as an experimental measure that he eliminate the use of sodium chloride as a condiment from the diet and replace it with the sodium malate mixture. After three months use of this material, the patient reported greatly relieved symptoms and a more liberal protein diet. He reacted favorably to the use of the condiment. On account of this, the authors began a system-

atic investigation of the action of the sodium malate mixture upon gastric acidity.

## EXPERIMENTAL

An artificial stomach contents was prepared according to the following formula<sup>2</sup>

Hydrochloric Acid	sufficient to make	1/40	per cent
Lactic Acid	sufficient to make	1/80	per cent
Butyric Acid	" " "	1/100	per cent
Acetic Acid	" " "	1/100	per cent
Pepsin, U S P		20	Gm
Rennin, N F		10	Gm
Sodium Chloride		0.1	Gm
Disodium Phosphate		0.1	Gm
Albumin		0.2	Gm
Glucose		0.1	Gm
Water	sufficient to make	1000	cc

This mixture was divided into 25 cc portions and different quantities of sodium malate mixture added to each portion. The total acidity was determined by titration using phenolphthalein as an indicator in the usual manner. The hydrogen-ion concentration was determined electrometrically using a Wilson<sup>3</sup> type hydrogen electrode. The results obtained are given in Table I.

Another sample of artificial gastric contents was prepared increasing the

TABLE I

No	Gm Sod Malate Mixture in 25 cc	pH	Degrees Acidity cc 0.1 N. NaOH to titrate 100 cc.	No
1	none	1.38	95	1
2	0.25	2.92	95	2
3	0.50	4.07	100	3
4	0.75	4.43	103	4
5	1.00	4.64	108	5
6	1.50	4.89	110	6
7	2.00	4.97	117	7
8	2.50	5.10	121	8
9	3.00	5.17	125	9
10	3.50	5.22	128	10
11	4.00	5.25	137	11
12	6.00	5.39	155	12

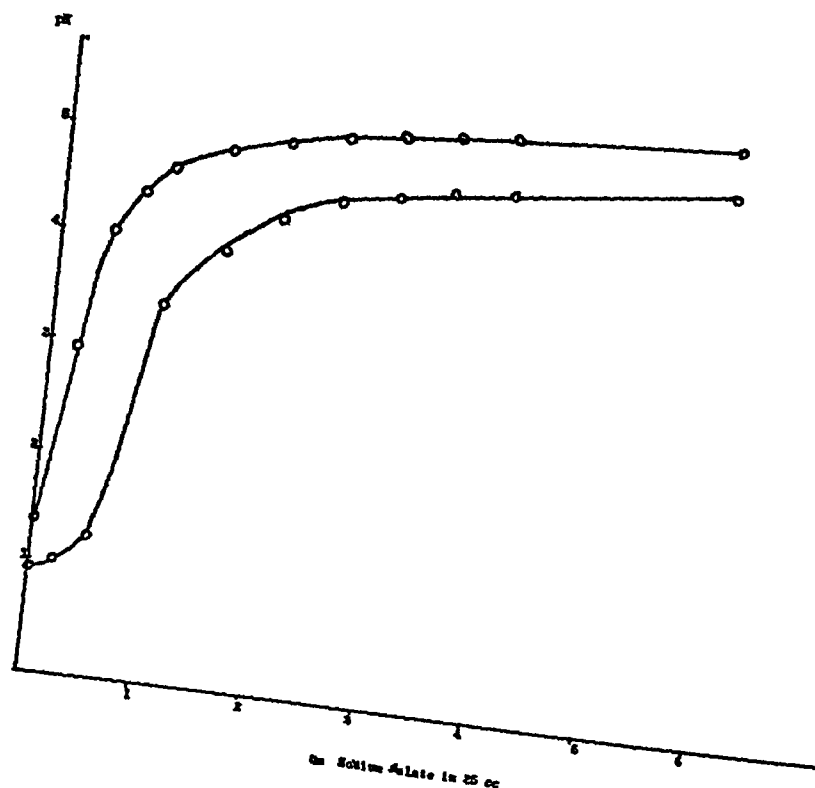
TABLE II

No	Gm Sod. Malate Mixture in 25 cc	pH	Degrees Acidity cc. 0.1 N NaOH to titrate 100 cc.
1	none	0.95	242
2	0.25	1.05	242
3	0.50	1.28	242
4	0.75	2.61	242
5	1.00	3.40	248
6	1.50	3.97	251
7	2.00	4.32	255
8	2.50	4.51	260
9	3.00	4.61	272
10	3.50	4.70	275
11	4.00	4.76	278
12	6.00	4.90	281

quantities of the four acids employed in the formula four fold. This more acidic mixture was subjected to the same procedure as the preceding one. The results are recorded in Table II.

The influence of sodium malate mixture upon the hydrogen-ion concentration of the gastric contents of the two different degrees of acidity can be readily observed from Graph No. I.

GRAPH NO. I



These experiments on artificial stomach contents indicate that the sodium malate mixture has a definite influence in reducing the hydrogen-ion concentration of the fluid. There is also observed a gradual increase in the total acidity. This we found to be due to some free malic acid in the sodium malate mixture which requires additional alkali for neutralization.

Having ascertained the influence of the sodium malate mixture upon artificial stomach contents, the procedure followed next was to determine its influence upon gastric acidity *in vivo*.

Nine individuals, whose history as far as gastric disturbances is concerned was negative, were given a test meal after a twelve-hour period of fasting. The meal consisted of two slices of wheat bread without crust and 500 cc of water. Forty minutes after the ingestion of the meal the stomach contents were removed by intubation and the hydrogen-ion concentration and total acidity determined as previously described. Table III records these results.

TABLE III

Individual	pH stomach contents	Degrees Acidity cc 0.1 N NaOH to titrate 100 cc
J	1.86	17
Fr	1.55	38
K	1.77	31
M	1.30	66
Jo	1.65	40
B	1.83	40
C	1.31	75
H	1.92	19
W	1.87	24
Mean	1.67	Mean 39

We considered the contents of the nine stomachs normal in view of the comprehensive work of Shohl and

King<sup>4</sup> in the Brady Institute of the Johns Hopkins Hospital. These investigators observed the limits of peptic digestion to be within the pH range 1.3 to 4.0 with an optimum at pH 1.65. On the following day seven of the nine individuals returned for a second intubation. The test meal administered this time was identical with that formerly given with the addition of six grams of the sodium malate mixture dissolved in the water. Under the same experimental conditions the results tabulated in Table IV were obtained.

TABLE IV

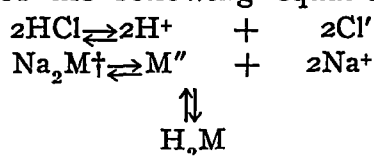
Individual	pH stomach contents	Degrees Acidity cc 0.1 N NaOH to titrate 100 cc
J	4.20	31
K	4.40	38
Jo	4.08	33
B	3.91	33
C	4.06	38
H	2.63	47
W	3.11	66
Mean	3.77	Mean 41

#### DISCUSSION OF RESULTS

From the experiments upon the artificial stomach contents, it is evident that the sodium malate mixture buffers the hydrochloric acid of the gastric contents. Furthermore, with as small a quantity as 0.25 gm of the mixture the pH (Table I) was changed from 1.38 to 2.92. It should be emphasized at this point that such a change in pH on the extreme acid range of the scale is very significant. Bearing in mind that pH is a logarithmic value, Gortner<sup>5</sup> has made the following interesting comparison. If the various points on the pH scale are

compared with cubical containers varying in size in similar numerical ratios, a pH change from 6 to 7 would be represented by a cube having an edge of  $\frac{1}{4}$  inch, whereas within the region of extreme acidity, say 1 to 2, would be represented by a cube with an edge 11  $\frac{9}{32}$  inches

The mechanism of the change in pH when sodium malate mixture is added can be readily understood by a study of the following equation



When sodium malate is added, the foregoing equilibrium is established. The reaction proceeds in the direction of free malic acid for it is the least ionized product. Thus theoretically the total acidity (with phenolphthalein as an indicator) will remain constant but the hydrogen-ion concentration will diminish upon the addition of sodium malate to gastric contents. Although Rehfuß<sup>6</sup> has pointed out, after a study of 800 gastric contents, that there is no degree of acidity found in disease that cannot be encountered in health, it is conceded that the determination of the hydrogen-ion concentration is probably the most significant measure of gastric acidity in suspected pathological conditions.

In the normal stomach contents examined (Table III) the probable error of the pH determinations calculated by the simplified formula

$$\text{P E} = 0.8453 \frac{\Sigma D}{N}$$

is 0.16 unit pH. A difference to be

<sup>†</sup>Where M represents the malic acid radical

significant must be at least three times the probable error or a difference of 0.48 pH unit. The mean of the pH of the stomach contents of the seven individuals after receiving the sodium malate mixture was 2.10 units pH higher. Therefore, the difference can be attributed to the influence of the sodium malate mixture. It is interesting to note that the means of the total acidities are not significantly different. This is what one might expect from the foregoing mechanism of buffering. This is dissimilar to the addition of a free base to the acid where actual neutralization would occur removing the hydrogen ions from solution by union with the hydroxyl ions of the base forming very slightly dissociated water. In the latter case a decrease of hydrogen-ion concentration would result also in a decrease in total titratable acidity. As the mechanism of the buffering action of this substance is different from the neutralization of the acid by free bases, carbonates or bicarbonates, it is possible that its use in the treatment of hyperacidity may not be accompanied by a subsequent increased secretion of hydrochloric acid as experienced when the ordinary alkalis are administered. Although 6 gm of the sodium malate mixture was administered to obtain the change in pH of two units, the authors attach much significance to the fact that with the artificially prepared gastric contents where natural variations in acidity and psychic factors are eliminated, a very small quantity of the sodium malate mixture produced a marked therapeutic change in hydrogen-ion concentration.

Shohl and King<sup>4</sup> in their investigations emphasize the significance of the

determination of the buffer value of gastric contents. They define the buffer value as the amount of acid or alkali necessary to be added to bring about a definite change in reaction. More recently Van Slyke<sup>7</sup> has comprehensively studied the capacity of buffer substances and by methods which were unequivocal arrived at a measure of the buffer capacity of solutions. The unit proposed by this

worker is the differential ratio  $\frac{dB}{dpH}$  which expresses the relationship between the increment in gram equivalents per liter of a strong base B added to a buffer solution and the resultant increment in pH. Using the measurable increments  $\frac{\Delta B}{\Delta pH}$  as sug-

gested by Van Slyke and used by one of us in other investigations (8, 9, 10) an average approximation of the buffer capacities of the gastric contents of these individuals without and with the sodium malate mixture can be determined.

In the titration of acidity with alkali hydroxide the faint pink color of the indicator phenolphthalein appears at pH 8.3. Let us assume that each titration was carried to this hydrogen-ion concentration. The average amount of tenth-normal sodium hydroxide required to change the pH from 1.67 to 8.3 is 390 cc per liter or 0.039 mole sodium hydroxide, therefore

$$\frac{\Delta B}{\Delta pH} = \frac{0.039}{6.63} = 0.0059$$

After the ingestion of the sodium malate mixture, 410 cc was the average

quantity of tenth-normal sodium hydroxide required to change the reaction from the average pH 3.77 to pH 8.3. Similarly this may be represented

$$\frac{\Delta B}{\Delta pH} = \frac{0.041}{4.53} = 0.0091$$

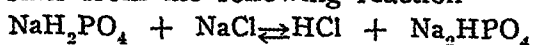
It is obvious that the buffer capacity of the gastric contents is increased by the addition of sodium malate mixture. We wish to emphasize that the buffer capacity is different at different points on the pH scale and these measurements serve only as comparisons. The evidence of the varying buffer capacity of the gastric contents may be ascertained by a study of the slope of the curves in Graph I.

#### SUMMARY

1. A study of the action of sodium malate mixture upon gastric acidity has been made in vitro and in vivo.

2. This substance possesses the capacity to reduce the hydrogen-ion concentration of gastric acidity and hence the opportunity for its use in hyperacidity is made available.

3. According to the theory of Maly<sup>11</sup> gastric hydrochloric acid results from the following reaction



If we accept this theory as correct the use of this sodium malate mixture as a condiment in cases of hyperacidity to replace table salt would seem to possess a two-fold advantage, first, the decreasing of the free gastric acidity and second, the elimination of a potential source of hydrochloric acid.

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# Tuberculin Therapy

By MILES J. BREUER, M.D., F.A.C.P., *Lincoln, Nebraska*

THE controversy over the efficacy of protein extracts of tubercle bacilli in the treatment of tuberculous patients, has seemed somewhat puzzling, and without solid ground to rest upon. Successful results are ardently claimed by some, and denied with equal emphasis by others. Usually this sort of a situation means that no rational basis has as yet been arrived at for the application of the treatment.

It is only very recently that we have acquired accurate knowledge of the principles underlying the reaction of the animal body to tubercle bacilli and tuberculo-protein. However, at present we have a sufficiently comprehensive conception of tuberculous allergy and tuberculous immunity to enable us to formulate at least a tentative working basis for the scientific use of tuberculin in therapy. Any such therapy must naturally be based upon and in accord with the facts of allergy and immunity as they have been learned from animal experimentation and pathological study, and with the principles that have been deduced therefrom. Therefore, a brief inquiry into these facts and principles is advisable in this place.

Immunity is that characteristic of the tissues by virtue of which tubercle bacilli are not able to survive there. A subject with good immunity survives infection with tubercle bacilli, whereas

one with low immunity dies quickly from the effects of such infection. The prompt death of non-immune animals does not at all involve the extensive presence of the well-known anatomical pathology of tuberculosis. Death takes place in a non-immune animal in the total absence of visible pathological lesions. Such lesions are due on the one hand to the allergic reaction to the tuberculo-protein, and on the other, to the foreign-body reaction of the tissues to the lipoid capsule of the tubercle bacilli.

Allergy is a sensitization of the subject's tissues to initial inoculation of tuberculo-protein, by virtue of which subsequent inoculations produce inflammation in these tissues. A first dose in a non-allergic animal, whether it be an injection from a needle or a natural infection, produces no observable effects, no inflammation, no symptoms, no visible lesions. But an effect has been produced nevertheless, for a second dose will produce all the well-known local and systemic inflammatory phenomena: hyperemia, exudate, fibrosis, or necrosis, fever, malaise, anorexia, nutritional disturbances. The nature and severity of the symptoms will depend on the degree of sensitization that has been established, and the size of the subsequent doses. The initial dose has in some way sensitized the body cells<sup>1</sup> so that they respond to



subsequent doses with the phenomena of inflammation. This sensitization is probably due to the development of antibodies which split the tuberculo-protein into toxic substances, but on that matter, knowledge is not as yet accurate.

A subject rendered allergic by initial inoculation, is also rendered to a greater or less degree immune. It will survive a larger dose of tubercle bacilli than it could have survived previous to the initial injection. Yet, immunity and allergy are not the same thing. They do not even run parallel, but are totally independent of each other. It merely happens that in many cases they are associated.

For example, if a subject is made allergic by inoculation with living tubercle bacilli, it will develop a much higher degree of immunity (survival ability) than if inoculated with dead bacilli or with tuberculo-protein. Dead bacilli do produce some degree of immunity, but from a practical therapeutic-value standpoint, only an insignificant one. Yet, the degree of allergy developed in either case, whether living or dead bacilli are injected, is precisely the same. It depends only on the amount of tuberculo-protein injected and on nothing else.

A high degree of allergy may exist in a subject that has little or no immunity. Infants infected with massive doses, or the tuberculosis of savages coming into city surroundings, are an example of this state of affairs. There is high fever, severe illness, extensive inflammatory pathology with exudation and necrosis, rapid course, and early death.

Conversely, we may have a low degree of allergy existing coincidentally with a high state of immunity. Willis<sup>2</sup> showed that guinea pigs after a lapse of two and a half years following an immunizing inoculation with tubercle bacilli, had practically lost all their allergic sensitiveness, but were still as highly immune as were the allergic control animals. Clinically, individuals are not uncommonly found harboring tuberculous pathology of considerable extent without any allergic symptoms, yet with sufficient immunity to continue to survive without suffering harm, and without even being conscious of their pathology.

Allergy and immunity may both be absent in an individual at the same time, as in the case of a guinea-pig that has been kept away from contact with tubercle bacilli. A dose of sufficient size will kill it promptly without any inflammatory reaction whatever. The two states may be developed to a high degree in the same individual, as in the commonly found clinical cases in which the patient is severely ill, with numerous inflammatory symptoms, and yet survives and eventually achieves a high degree of recovery.

Tuberculin, which is the protein extracted from the bodies of tubercle bacilli, has exactly the same effect on injection as do the dead bacilli, with the exception that the tubercle-forming reaction due to the presence of the lipid capsule is lacking. The effect of its injection into the animal body is, initially, to produce the allergic state. Subsequently, the injection of a large dose will produce a severe reaction, with inflammation, exudation, and necrosis. But, a series of smaller

doses, properly graduated and timed will de-sensitize the individual and diminish the allergic state, so that larger and larger amounts of tuberculo-protein can then be administered without systemic or local disturbance.

It was stated above that the injection of tuberculo-protein has on *immunity* only a negligible effect. There is some disagreement among workers in this field as to whether it will produce any immunity at all. Krause denies it<sup>3</sup>, whereas Petroff and Stewart<sup>4</sup> find that some degree of immunity is produced, but agree that it is very slight indeed, certainly not of sufficient importance to be a consideration in clinical therapeutics.

Therefore, if tuberculin is to be used clinically, in the treatment of tuberculous patients, it cannot be for any effects that it may have in increasing immunity. It will do little or nothing to prevent the bacilli from killing the patient, it will not prevent reinfection or additional infection. It can only be used to reduce allergic sensitization.

Allergy, however, is at the bottom of a large proportion of the patient's illness and clinical symptoms, of his distress and discomfort. His fever, his malaise and reduction of capacity for effort, his lack of appetite and loss of weight, are all allergic phenomena. Allergy is responsible for the inflammatory process with its exudation and its necrosis. The whole "toxic" and inflammatory picture is due to allergy. It is completely absent in non-allergic animals dying from lethal doses of tubercle bacilli.

It would be of immense value to the tuberculous patient if he could by some means be relieved of this burden of

distress and this load of inflammation. Even though such means might possibly not be curative, nor life-saving, nevertheless it would be of distinct benefit. The patient could be made comfortable and useful. The relief of distressing symptoms is equivalent to reduction of stress for the patient, and reduction of stress is one of the chief considerations in the treatment of the tuberculous patient, and one of the greatest contributions toward recovery.

*A priori*, therefore, tuberculin should be indicated in those cases whose symptoms are chiefly of allergic origin, i.e., those which are inflammatory in character, or connected directly or indirectly with inflammatory processes.

In selecting cases for such treatment, the distinction must be observed between symptoms of allergic origin, as already enumerated, and those of reflex origin. Pains and functional disturbances in the viscera, the heart, larynx, stomach, large and small intestine, uterus, could hardly be expected to receive direct benefit from tuberculin treatment. These symptoms are of neurological nature, due to the existence of definitely established abnormal paths for nervous impulses. It is necessary to recognize their essential difference from allergic symptoms in selecting cases for tuberculin treatment. Yet, as their source is originally a localized inflammation that has set up the irritation within the nervous system, ultimately the control of the inflammation ought to furnish the hope of relief even for the abnormally functioning reflexes.

About a year has passed since these ideas were definitely crystallized. Dur-

ing that year the writer has had the opportunity of selecting twenty-six appropriate cases, and studying the effect of tuberculin treatment with this idea in mind. The following observations were made:

The cases were all controlled cases, as they had previously failed to respond noticeably to general therapeutic regimen. None of them were severe nor advanced cases. Treatment was in each case begun with 0.00075 mgm of Mulford's Old Tuberculin, and continued empirically, the size and frequency of dosage being determined by the patient's reactions and his increase in tolerance.

- 14 cases clinical symptomatology purely allergic
- 11 cases mixed with reflex symptomatology, reflex in minority
- 2 cases unable to obtain any desensitization, unable to increase dosage or to continue treatment. Reason unknown
- 4 cases impossible to obtain sufficient control over patient's behavior to render observation of any value, the unknown amounts of tuberculin liberated by excessive physical activity obscured results
- 20 cases tolerance to tuberculin raised so that within 2 to 5 months, 15 mgm of tuberculin could be injected without more than moderate reaction
- 4 cases original temperature of patient remained unchanged in spite of increased tolerance to tuberculin
- 6 cases temperature reduced to normal
- 11 cases temperature lowered by 1 degree or more, though not brought to normal
- 16 cases gain of 5 percent or more in weight
- 4 cases gain to standard weight
- 16 cases distinct decrease in malaise and fatigue, improvement in physical state

8 cases reduction of pulse rate from near 100 to near 80

5 cases change for the better in local physical findings: râles, respiratory movements, nutritional state of shoulder-girdle muscles, localized density, etc.

5 cases (out of a total of only 6 who were checked two or more times by X-ray) definite change toward the fibrosed type of X-ray shadow

19 cases one or more signs or symptoms of improvement

6 cases improved condition maintained for 6 months without further tuberculin treatment, but with adequate hygienic precautions

At first glance, the amount of improvement obtained may not seem anything revolutionary, or vastly different from previously reported figures. But when the fact is taken into consideration that these are thoroughly controlled cases, which previously failed under all other efforts, and which improved under no other additional method than the tuberculin, and that they were selected for their allergic symptomatology, the results are suggestive.

I have been able to go back over my records for nearly ten years, and make an accurate analysis of tuberculin therapy instituted during that period. This was the period during which I have been using a standardized record-form for recording history, examination and treatment.<sup>5</sup> During this period I find 181 cases treated with tuberculin. Seventy-nine of these showed improvement attributable to tuberculin, and of this 79, 41 showed very satisfactory results or arrest. The significance of this 22 per cent of satisfactory results among improved cases, is modified by two factors: approxi-

mately 50 per cent of the 181 cases were only slightly or moderately advanced, since during this period we have been trying to make a point of early diagnosis, secondly, in addition to tuberculin treatment, every other possible therapeutic means was used. Thus of course increases the significance of the figures in the previous group, which were selected as not having responded to general treatment.

In all of these 79 cases, allergic symptoms were a prominent feature:

Fever of 100 or more	79
Subnormal weight	74
Anorexia	77
Râles	64
Localized density	48
Exudative X-ray shadow	21
Reduced effort capacity	78
Tachycardia	70
Headache	27
Malaise	74

In the 102 cases in which the results of tuberculin treatment were unsuccessful or unsatisfactory, the signs and symptoms of the visceral-reflex type predominated:

G-I symptoms, irritative type	69
G-I symptoms, atonic type	12
Asthma	4
Chest, back, and arm pains	60
Vague abdominal pains	22
Pains in occiput and neck	46
Menstrual colic	4
Bradycardia	4
High nervous drive (low basal rate)	12
X-ray shadow limited to fibrosis	21

The two groups of cases compare as follows:

#### Improvement noted

43.6 percent in unselected, uncontrolled cases

76.0 percent in allergically selected, controlled cases

In this latter group, 16 percent failed to receive benefit from tuberculin because of environmental factors, and only 8 percent because of failure of the tuberculin to work properly.

This report is preliminary and can only be suggestive. Further observation on a larger number of cases is required to test the validity of the theoretical considerations, and to develop skill in handling various phases of the therapeutic method, such as selection of cases, graduation of dosage, etc.

#### SUMMARY

1 The effect of tuberculin is to decrease the patient's allergic sensitization.

2 Its effect in increasing immunity is negligible.

3 Clinically it ought to be useful in those cases in which the allergic state is principally at the basis of the patient's symptomatology.

4 A series of 26 previously unresponsive cases selected for treatment with this distinction in view, showed no contradiction and probable confirmation of the above idea.

5 Analysis of 181 unselected cases previously treated, also confirms the idea.

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# Present Status of Heliotherapy in Tuberculosis\*

By CHARLES K. PETTER, M D , *Glen Lake Sanatorium, Oak Terrace, Minnesota*

*"'Let there be light,' said God, and forthwith light  
Ethereal first of things, quintessence pure  
Sprung from the deep"*

MILTON'S quotation exemplifies the aphorism that light is life. Metabolism and the vital processes of higher organisms are impossible, while our material universe could not have developed, without light. Every race of man has looked upon the sun as a god of comfort, health and life. Little wonder is it then that the earliest written histories of the Egyptian, Babylonian, Iranian-Persian, Greek, Roman and Hebrew peoples refer to the sun first as a source of light, then as the deity of health and life. (Aton, Baal, Mithra, Apollo and Helios are the names given these various deities.)

Coming on down through the ages we find discussion of heliotherapy procedures by such men as Herodotus, Hippocrates, Celsus, Galen and Cicero. In the middle ages Avicenna recommended sunbaths for his patients while Paracelsus first recommended mountain climate as most suitable for sun cure.

Nothing much further appears until an awakening of interest in helio-

therapy took place on the part of the French, when Rousseau called attention to the potentialities of sunlight in 1735. In 1815 Cauvix published a paper in which he says, "Speaking of scrofulous infants, send them to the country, feed them up as well as possible, but above all, make them roast, burn and roast in the sun." Ollier and Poncet of Lyons treated tuberculous arthritis by sunlight in 1840.

The further development of modern heliotherapy has taken place particularly through the efforts of Bernard, Rollier and Finsen. Finsen was the pioneer in artificial heliotherapy while as Guavaix says, "Rollier is the 'High Priest' of modern sun worship, he has led us back to sunshine and simplicity, to the first principles of light and life."

One cannot discuss heliotherapy without at least a brief consideration of the physics involved. Light has been defined as "an electromagnetic disturbance of the ether" (Lodge). The electromagnetic vibrations which pervade our universe when arranged according to wavelengths present a definite spectrum. At one extreme the waves are measured in ten millionths of a millimeter while at the other end

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\*Read before the Meeting of the Resident and Consulting Staff Glen Lake Sanatorium, Oak Terrace, Minnesota November 19, 1930

of the spectrum hundreds of meters  
express the wave lengths (Figure 1)

In addition to wave length, these ethereal agitations possess a velocity of 186,300 miles per second and a frequency varying inversely as the wave length. This entire electromagnetic spectrum if projected as one view, with the visible part one foot in length, would be seven million miles long. At one end are the recently observed cosmic rays and at the other the Hertzian or radio waves, with gamma and X-rays, ultra-violet, visible light, and penetrating heat or infra-red rays in between. (The Angstrom unit, one ten millionth part of a millimeter, has been accepted as the unit of measurement.)

We are particularly interested in a combination of the near ultra-violet

and the visible spectrum in treating tuberculosis

Although many people believe the beneficial effects of heliotherapy due to the ultra-violet component, I believe that conclusive evidence has been presented by many observers to show that wave lengths of 3900 to 8000  $\text{\AA}$  (visible) are a necessary adjunct to the biotic or vital rays, (2800-3800  $\text{\AA}$ ), in other words, a spectral range from 2800 to 8000  $\text{\AA}$  whether from the sun direct or from an artificial source (carbon arc) is the agent of choice

Radiant energy in the range mentioned (2800-8000 Å) produces very definite physiologic effects, some due to the ultra-violet alone, others to the visible alone and still others to the entire range. These effects are briefly

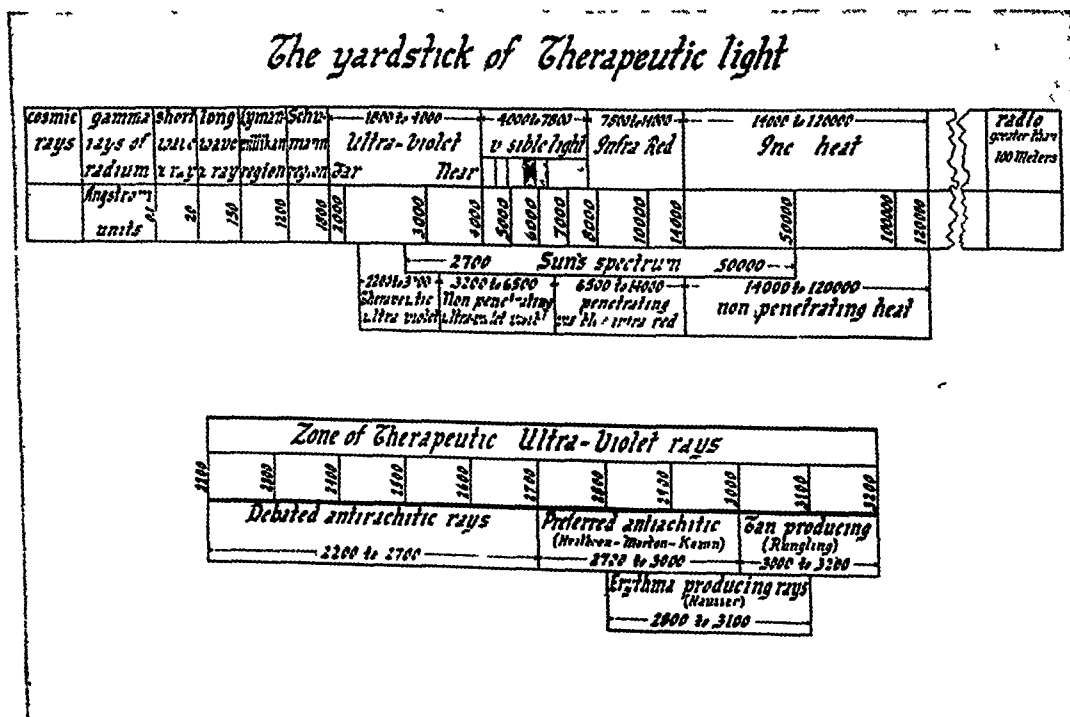


FIG 1 Diagrammatic representation of electromagnetic spectrum, showing wave lengths in Angstrom Units

1 Erythema and slight tanning accompanied by improvement in the health, texture and function of the skin

2 In the blood there is an increase in hemoglobin, a rise in red count and platelet count. The lymphocytes show an initial drop following irradiation with subsequent rise while the polynuclear elements are increased

3 The calcium phosphorus balance is brought to normal

4 Blood pressure tends to become lower, while pulse rate shows an initial rise with subsequent drop to normal or below

5 Body temperature experiences an initial rise but returns to within one degree of normal shortly after irradiation has ceased

6 Basal metabolic rate is not increased but elimination is aided. Blood urea nitrogen is reduced and nutrition improved

7 Muscles experience an improvement in tone, contour and nutrition. Rollier has referred to sun bathing as the best masseur one can employ

8 Healing is stimulated and tuberculous processes affected quite specifically

9 There is probably a definite chemical effect on the blood, the rays penetrating to the capillaries where their energy is absorbed by the blood stream and effects produced on distant tissues and organs

10 Sunbaths produce the liberation of varying amounts of tuberculin and thus act the same as work on the tuberculous process. Graduated doses of light liberate controllable amounts of tuberculin while physical activities may produce more than is desired

The present day popularity of both natural and artificial irradiation as a beneficial measure has led to much injudicious use of this therapeutic agent. Edgar Mayer has stated in this connection, "Light of any form by itself is not curative, but comprises only one of the important adjuncts in the treatment of tuberculosis. To believe that sunlight or artificial sources of light will cure all forms of surgical tuberculosis, to be unduly optimistic about this treatment and to consider it a specific form of treatment, to use it without sound medical guidance and adequate equipment, and finally to employ it to the exclusion of rest and hygienic regimen, eliminating orthopedic measures or the occasional necessary surgical intervention in bone and joint tuberculosis is bound eventually to dishearten many sufferers and to bring discredit on an otherwise desirable method of treatment."

Let us then be a bit conservative in our properly enthusiastic application of heliotherapy in tuberculosis

If we follow the plan outlined by Watson (figure 2) untoward results will be avoided and a rational system of heliotherapy carried out

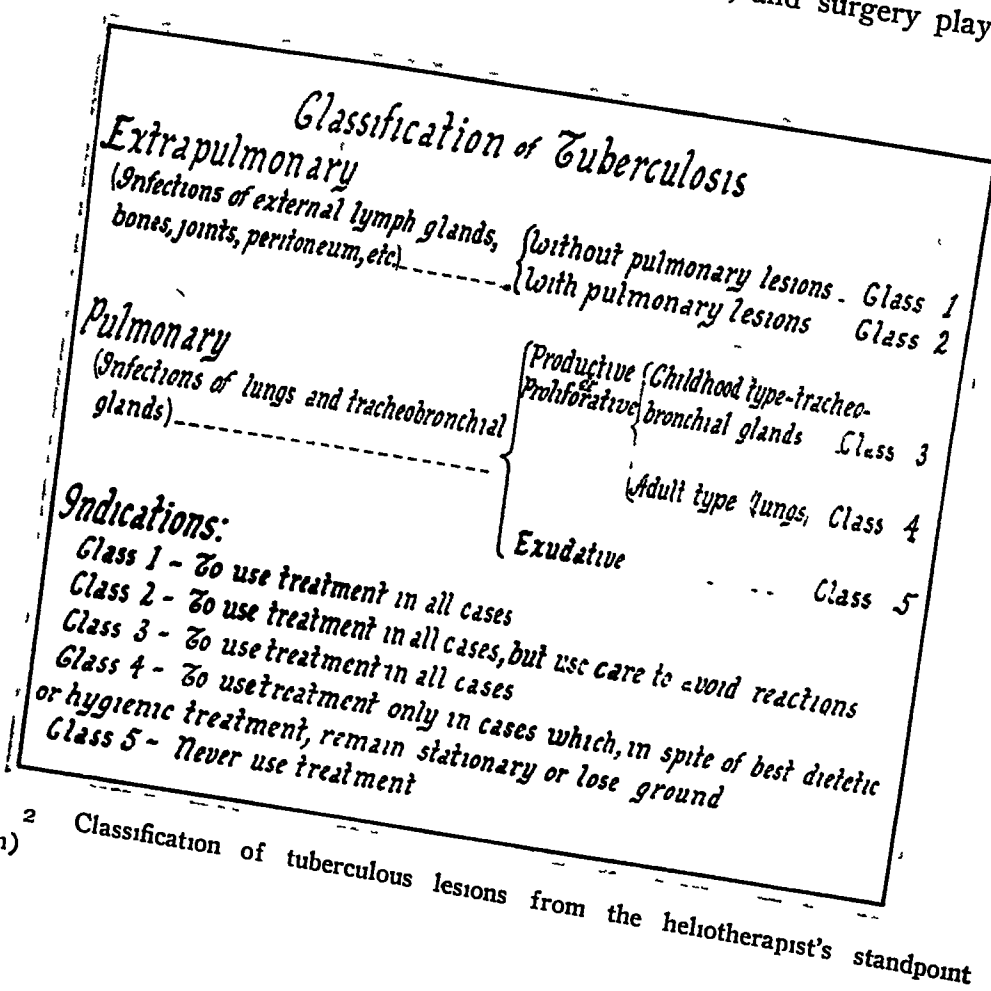
The child with tracheo-bronchial glandular tuberculosis presents a very definite indication for heliotherapy and the treatment will give him the maximum insurance against future disability from tuberculous disease

In the treatment of the adult form of pulmonary tuberculosis with heliotherapy, much unnecessary fear and unjust criticism of this therapeutic agent has arisen. True, every case of pulmonary tuberculosis cannot be given sunbaths, in fact, only a minority of

these patients can be so treated. Yet hemoptysis, miliary dissemination and the spread of lesions in the lung are not encountered where the case is properly selected and supervised. The patient with an exudative lesion, who may be acutely ill with definite pyrexia and toxemia should never be given heliotherapy but the one with a fibrotic lesion and positive sputum, or a case not improving on rest and hygienic treatment may be given sunbaths to good advantage under adequate medical supervision. In my talks to medical students I list pulmonary tuberculosis as a contraindication to heliotherapy in order that they may err on the safe side if they err at all.

In these pulmonary cases we may expect (1) improvement in general condition, (2) decrease in lung moisture, "râles", (3) decrease in sputum, it very often becoming negative, and (4) increased fibrosis.

Bone and joint tuberculosis presents probably the largest group of extrapulmonary cases which we are called upon to treat. The majority are accompanied by pulmonary lesions of varying degrees of severity. This factor alters the procedure of the heliotherapist only very slightly, as we have found that with proper treatment of the bone lesion, the pulmonary focus responds favorably as a rule. Orthopedic measures must never be overlooked, and surgery plays a defi-





nite part in treatment Before any surgical procedure is instituted, heliotherapy should be carried out for several months in order to bring the lesion to a quiescent state, if possible Fusion and ankylosing operations and arthrodeses should then be followed by several more months of heliotherapy for the operation as such rarely removes the tuberculous focus but only gives added fixation to the joint involved In the case of concomitant abscess and sinus formation these lesions repair quite readily under the influence of radiant therapy Except in extremely early cases of joint tuberculosis, where erosion of the cartilage and destruction of bone has not as yet occurred, no attempt is made to secure a functioning joint Where there has been bone destruction a firmly ankylosed joint gives much more insurance against future recurrence than a partly movable one

Heliotherapy alone as an adjunct to rest and hygienic measures plus orthopedic sense gives good results, but only after an extremely long period of hospitalization On the other hand, it is very necessary to return adults to industry as soon as possible, so the practice of aiding the above measures by a proper surgical procedure, and thus shortening disability, is becoming more and more the accepted policy

Tuberculosis of superficial lymph nodes with and without softening and sinus formation responds well to heliotherapy General body irradiation is the procedure of choice It has been our practice to supplement heliotherapy with local X-ray to the glands involved This hastens fibrosis and shortens the time required for cure

Tuberculous pleuritis, with effusion, while an accompaniment of pulmonary tuberculosis, often clears with the aid of sun baths and I believe every case of pleural effusion (tuberculous) unless accompanied by a florid pulmonary lesion should have heliotherapy This measure is reported as effective in preventing and remedying a tuberculous empyema

Tuberculosis of the peritoneum is a secondary manifestation of a tuberculous lesion in the bowel, intra-abdominal or pelvic lymph nodes or pelvic organs Rest and hygienic treatment plus heliotherapy over many months will produce a marked reduction in symptoms and local signs Often it is possible, when the peritoneal lesion has become quiescent, to remove the primary focus, such as tube or appendix for instance, and then have the peritoneal process heal under a few more months of treatment

Genito-urinary tuberculosis presents a complex picture unless the infection is unilateral or limited to a single organ which may be extirpated When a unilateral renal tuberculosis is proven, the patient should have (1) heliotherapy during study, (2) the nephrectomy, and (3) further heliotherapy Tuberculosis of both kidneys, or of the bladder or genitalia, demands prolonged rest and heliotherapy Local lesions of epididymis may of course be removed, but the frequent complication of prostatitis, cystitis, or seminal vesiculitis calls for a long post operative course of treatment

Tuberculosis of the skin in this country does not present the problem that it does in Europe However, it is usually a local manifestation of a

systemic disease and, while not requiring as much rest therapy as do some other lesions, responds remarkably well to heliotherapy

In treating local lesions of the middle ear, larynx and eye, as well as ulceration of the anus and lower rectum and lesions of the skin, the Kromayer lamp has proven of definite value as an adjunct to hygienic and rest treatment. In some European clinics these lesions are not treated locally at all but the patient is given general body radiation from the sun or carbon arc, with equally good results

When one attempts to administer radiant energy as a therapeutic agent there are certain important factors which must not be overlooked. First of all, each patient is a new problem in therapeutics from the heliotherapist's standpoint. No two people react exactly the same to equal doses of light nor do two cases of tuberculosis present the same clinical features. Therefore, although an arbitrary plan of dosage may be adopted, the heliotherapist must individualize, and not attempt to carry through the same routine for every case. Secondly, too much irradiation, instead of being beneficial will be harmful by setting up reaction. The third factor to be observed is the reaction of temperature and pulse rate following irradiation. Immediately after an exposure to the sun, an elevation of body temperature is noted, which may reach one degree or more above normal. This must drop back to within one degree of normal within a half hour or the reaction is considered unfavorable and subsequent dosage must be reduced or insolation stopped entirely. We have

treated patients who could not take larger exposures than one minute at the start without reaction but who were able to gradually increase this and progressed satisfactorily. The pulse rate is likewise elevated after insolation. We require that within one half hour after exposure this rate must return to within twenty beats of its preinsolation rate. The body temperature and pulse reaction plus general condition of the patient, then, serve as our important "checks" on the progress of the treatment.

Rollier drew up an arbitrary norm which serves as the foundation for all heliotherapy prescriptions (Figure 3). His plan is to divide the body into five zones and expose each zone for a period of five minutes anteriorly and posteriorly until the patient is receiving a total of two to four hours insolation each day. The total varies with atmospheric conditions, the individual patient and the individual therapist. Some therapists advocate single daily exposures of two to four hours while others prefer shorter exposures, say forty-five to ninety minutes repeated after a period of rest. We feel that the exposures should be so regulated that tan production does not become intense. A ruddy erythema just bordering on a mahogany color is preferable to a tan which becomes almost chocolate brown, for this latter filters out a large part of the ultra-violet which we wish to have absorbed by the blood stream.

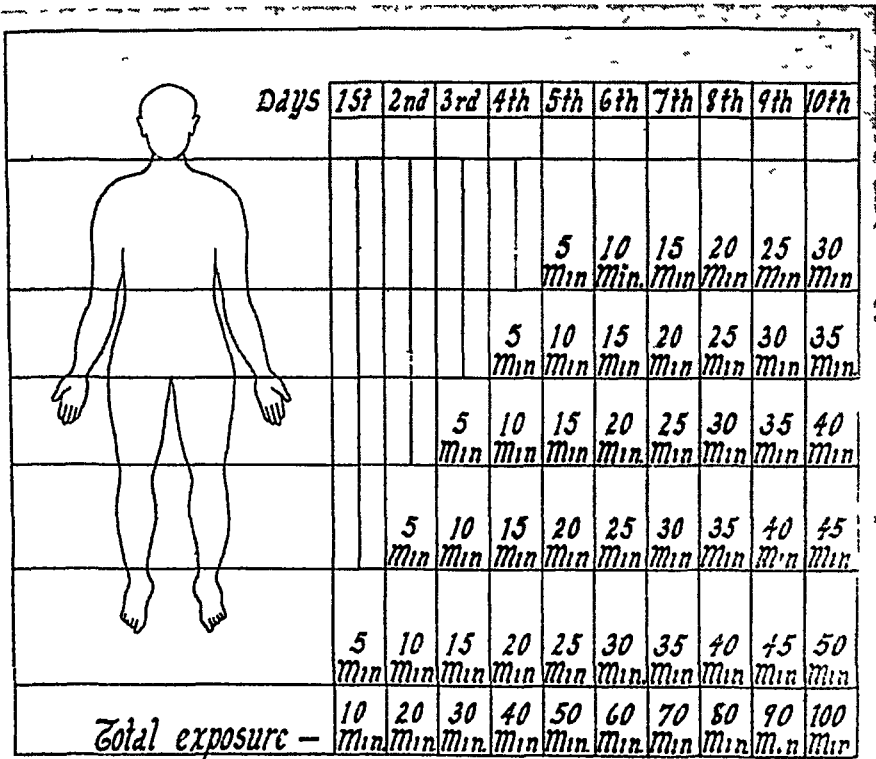
The question of the mercury arc versus the carbon arc is one which we believe can be definitely settled. It has been our experience that at the end of the sun season, patients are in much

better condition than they are in the following spring after several months of quartz mercury arc irradiation. On the other hand, a few patients who have had carbon arc irradiation have continued to progress during the winter months just as they did under solar irradiation. Since the mercury arc spectrum is rich in the short ultra-violet 2500 to 2700 A° and feeble in the range from 2800 to 3000 A°, and because the carbon arc using Sunshine Carbons gives a spectrum similar to that of the sun, 2800 to 8000 A°, we feel that the carbon arc is the artificial source to be preferred.

SUMMARY

I Heliotherapy then is an important and necessary adjunct to the rest and hygienic treatment of tuberculosis

- 2 It must not be overdone
- 3 Patients must be insulated only under observation
- 4 Graduated daily exposure individualized for each case must be the procedure of choice and safety
- 5 Selected cases of pulmonary tuberculosis may safely be irradiated with benefit
- 6 Extrapulmonary tuberculous lesions are definite indications for heliotherapy
- 7 The part of the electro-magnetic spectrum from 2800 A° (near ultra-violet) to 8000 A° (visible red) is that part which we believe to be the most beneficial in treating tuberculosis and therefore the carbon arc lamp is preferable to the quartz mercury arc



From the 10th to the 15th day, increase according to same scale. From the 15th day, all the previously exposed portions of the body should receive the same amount of insulation as the longest exposed part,—increasing the time 5 minutes daily, till a bath of from 3 to 4 hours is taken.

FIG 3 Schedule of daily exposure for heliotherapy (Rollier)

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# Mild Hyperthyroidism and the Neuroses\*

By PHILIP S SMITH, M.D., F.A.C.P., *Abingdon, Va*

**N**O APOLOGY will be made for bringing to your attention a subject so frequently discussed in recent years as hyperthyroidism. Until the essential facts, both physiologic and pathologic, are more completely understood, the theme is not inappropriate for further study

The caption of the paper suggests the limitations of the subject to be considered. That a well-defined and advanced hyperthyroidism presents no difficulty in diagnosis is indicated by the fact that pupil nurses frequently classify the patient upon admission to the hospital before the preliminary notes are made by the interns. In these patients thorough clinical investigation merely confirms the tentative diagnosis and affords an opportunity to estimate the degree of toxicity and the presence of visceral complications of the disease. Furthermore, an intensive study usually enables one to differentiate the two common types of hyperthyroidism—toxic adenoma and exophthalmic goiter, involving factors of importance in prognosis and possibly treatment.

Every well equipped hospital and,

in this section of the State, practically every physician of average experience, is familiar with the acutely toxic patient. Equally, if not more numerous is that group with indefinite or incomplete evidence of thyroid overactivity presenting a much more difficult diagnostic problem.

It is my purpose to discuss briefly some phases of the similarity of mild hyperthyroidism and the conditions generally described as neuroses and psychoneuroses.

Of the intimate inter-relationship existing between the functions of many of the ductless glands there is ample proof. Unfortunately for the patient and the medical profession, this fact has been capitalized by many manufacturers and dispensers of so-called "pluriglandular" products with attractive, but unscientific, arguments supporting their therapeutic employment. But this does not invalidate the evidence of a common factor, such as sudden fright or great emotion, augmenting conjointly the activity, for example, of the thyroid and suprarenal glands during the period of stress. In such functional states the rôle played by the autonomic, or vegetative, nervous system is fairly well understood.

In the less sudden and acute conditions that provoke chronic fatigue, worry, anxiety, introspection, depres-

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†From the Johnston Memorial Clinic, Abingdon, Virginia

sion and hysteria there is also evidence oftentimes of a disturbed endocrine gland function influencing the sympathetic and vagal nerves, the converse also seems to be equally true. Just as the acute emotional states resemble in many respects traumatic or surgical shock, so the less pronounced psycho-neurotic conditions have been termed "chronic shock."

For several years I have been interested in studying patients with exophthalmic goiter from the standpoint of a provoking factor of which the patient was conscious. We are familiar with the apparent sequence of a systemic infection and the inauguration of symptoms of Basedow's disease. In my experience where the exciting cause can be definitely elicited, it has been more frequently a sudden mental or nervous shock or "insult." An industrial disaster in a nearby town causing the death of many and vast property loss was offered by two patients as the explanation of the onset of their symptoms. Another woman dated her alleged "nervous breakdown" from a negro unexpectedly appearing at a nearby open window while she was using the telephone. These patients when examined some months later presented the classical picture of a high-grade exophthalmic goiter.

In 1926 I reported a review of a group of hypothyroid patients, of whom twelve young females had most of the symptoms and signs usually associated with a hyperthyroid state. All had lowered metabolic rates.

But I am considering now neither the acutely toxic patient nor the moderate hypothyroid, but rather those who give histories of nervousness, loss

of weight, goiter, tachycardia, palpitation, tremulousness, emotional instability and oftentimes diaphoresis, with slightly elevated metabolic rates.

Previous to the development of indirect calorimetry these individuals were oftentimes subjected to the "Goetsch test." If there was an unusual response to the subcutaneous injection of epinephrine, the thyroid gland was usually indicted as the cause of the patient's symptoms. Many such individuals, doubtless, were victims of a functional nervous condition associated with a pre-existing excessive function of the suprarenal glands. If so, their reaction to the injected agent can readily be explained.

Valuable as is the metabolism apparatus in differentiating the borderline hyperthyroid patient and the psycho-neurotic, too much reliance can be placed in one series of tests. It is well known by those who have conducted many metabolic tests that neurotic individuals are prone at first to give moderately elevated rates. Their co-operation usually is poor and it is difficult for them to relax sufficiently to meet the requirements of a basal state.

With a view to enhancing the importance of the clinical investigation and evaluating the symptoms and signs of these patients, Dr. James H. Smith, of the McGuire Clinic, has formulated and employed the following table of relative values arbitrarily assigned.

Nervousness	1
Tremor (fine)	2
Loss of weight (5% or more)	3
Tachycardia (90 per min or more)	4
Exophthalmos	5
Goiter	6
	—
	21

He believes that if the total result of the above values in a given patient exceeds 10 the diagnosis of hyperthyroidism is fairly well established and the metabolic rate will usually be found above plus 20. The above formula is of undoubted value, but in a country where adolescent thyroid enlargement and simple goiter are quite common, neurasthenic individuals are frequently seen who may have all of the above findings except exophthalmos. They often have a slightly elevated metabolic rate at the first observation, but subsequently are found to have no primary thyroid disease of an organic type. Many of these patients have been advised that their goiter is responsible for their symptoms, and the consequent fear of operation or long periods of disability brings them to the physician or surgeon for advice. Others have harbored for years morbid fears of other diseases.

Many neurotic patients are young women who have been married within recent years. The roseate glow of the post-marital stage has been replaced by the advent of children, worries and apprehensions. Confining and burdensome housework and oftentimes insufficient funds with which to balance the family budget result. Confronted with daily problems of this sort, with no solution to rectify them, a vicious circle is established. Such individuals, especially if they have a friend or relative who has a toxic goiter, may simulate unconsciously the hyperthyroid symptoms in a remarkably accurate manner. The premature suggestion of the family physician that possibly the goiter present since childhood or adolescence may be responsible

for their symptoms greatly adds to the difficulty. If a single metabolic test is done, the resulting rate, in the absence of a basal state, is apt to be slightly or moderately elevated. The administration of an iodine solution at this stage further confuses the clinical problem. A subtotal thyroidectomy will probably sentence the patient to a long term of invalidism with the same symptom-complex as previously.

During the past year I have been impressed with the increasing number of patients with such a syndrome coming to my attention. The recent industrial and financial depression may be a contributing explanation. Some of them were young married women who at the time of examination, or subsequently, were found to be harassed by marital unhappiness having a sexual basis.

No diagnostic "yardstick" is applicable to all such patients. Each one presents individual problems for solution. Disappointments naturally are encountered in apprehending the causative factors in some and their removal in others.

The investigation involves much patience, painstaking effort and sufficient time. Nothing, I believe, is more essential than a carefully recorded, detailed history of these individuals. The probability of successfully ferreting out the latent or occult contributory causes, of which the patient herself may not be conscious at the time, is increased if the family and friends are excluded. Otherwise the patient is apt to repress some confidential matter of importance. One such, a young married woman, who denied repeatedly in the presence of

her husband any marital or domestic difficulties, later wrote me of her restraint and reticence. When her husband's attentions to a neighboring feminine competitor of his wife ceased, the latter's thyroid symptoms and slightly elevated metabolic rate promptly disappeared.

The physical examination of these patients is of equal value in arriving at a correct estimate of the problem. Are the complaints of tremulousness, tachycardia, diaphoresis, etc., confirmed? Does the goiter present a bruit, thrill, and has it other characteristics of a toxic adenoma or hyperplastic thyroid? Is the systolic blood pressure increased—the patient's age and other factors generally associated with a systolic elevation considered? This point I wish to stress. The blood pressure observation should be repeated, if initially elevated, until it can be read with the patient relaxed, otherwise the increased pulse pressure may be influenced by psychic factors. The frequent association of an increased pulse pressure with hyperthyroidism is important and not generally considered. Its absence lends weight to a functional state. The chart will illustrate this point. The exceptions found in both groups will indicate that the cases were not selected, but chosen at random. The tables give more detailed information regarding the fifty patients composing each group. It will be noted that the average pulse pressure of the hyperthyroid is 25 mm (or approximately 65 per cent) greater than that of the average neurotic patient. As expected, the average age of the toxic goiter patient is greater than the neurotic. The fre-

quent association of chronic foci of infection in both groups is interesting and of significance therapeutically.

After the foregoing statistics were compiled, the following statements by Dr. W. M. Boothby came to my attention:

1 "As pointed out by Plummer, adenomatous goiter with hyperthyroidism is not infrequently associated with hypertension as evidenced clinically by an elevated diastolic blood pressure ranging from 85 to 120 mm."

Only one of our fifteen cases of toxic adenoma charted had a diastolic pressure above 90 mm.

2 "In the absence of hypertension (diastolic), there will be an increase in the systolic and pulse pressures commensurate with the increase in metabolism."

With a few striking exceptions, this observation is confirmed in the cases of toxic adenoma shown.

Referring to patients with exophthalmic goiter, Dr. Boothby further states:

1 "If the diastolic pressure is low, the systolic pressure may be either normal or slightly increased. On the other hand, if the diastolic pressure is normal or increased, the systolic pressure will be distinctly elevated, as a high pulse pressure is necessary in order that the increased blood flow required by an elevated metabolism may be maintained."

Of the thirteen patients with exophthalmic goiter having diastolic pressures less than 80 mm, eight (61.6 per cent) show systolic pressures 140 mm or above. Of the remaining twelve cases with diastolic pressures 80 mm



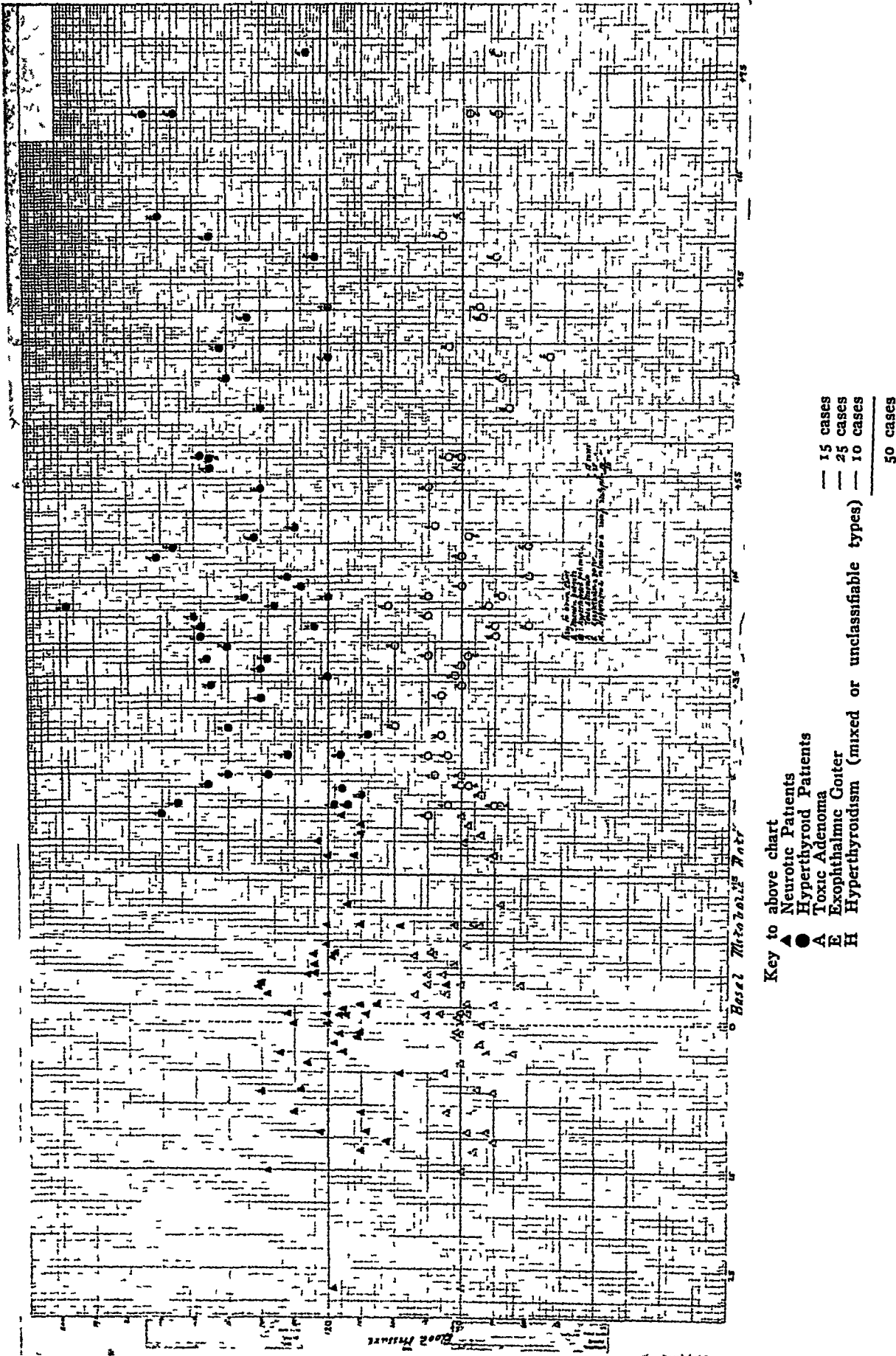


TABLE NO 1—NEUROSES

CASE	SEX	AGE	SBP	DBP	PULSE METABOLIC		COMPLICATING DISEASES —
					PRESSURE	RATE	
1	F	21	118	88	30	+ 7%	Chr tonsillitis, myocarditis
2	F	55	140	90	50	+ 4%	(Chr tonsillitis, visceroptosis, mucous colitis)
3	F	23	114	78	36	+ 1%	None
4	F	17	138	80	58	—15%	Hypothyroidism
5	F	20	116	80	36	+ 1%	Malnutrition
6	F	17	110	78	32	+20% (?)	(Goiter, arrested mental development, intestinal parasites)
7	F	24	120	74	46	0	Chr tonsillitis
8	F	17	128	85	43	— 7%	(Chr tonsillitis, appendicitis, Eye-strain, cardiospasm)
9	F	24	110	80	30	— 1%	Chr tonsillitis, aerophagia
10	F	27	112	70	42	+17%	Hyperthyroidism (?)
11	F	35	98	85	13	— 5%	(Chr tonsillitis, pyorrhoea, chr pelvic infection)
12	F	21	124	85	39	+ 5%	(Goiter (simple), chr tonsillitis, eye-strain)
13	F	37	118	74	44	— 2%	Chr tonsillitis, appendicitis
14	M	41	114	68	46	+12%	Chr tonsillitis, myocarditis
15	F	36	120	82	38	+10%	Chr tonsillitis, appendicitis
16	F	39	138	94	44	— 3%	Menopause
17	F	32	110	74	36	+19%	(Chr tonsillitis, sinusitis, hyperthyroidism (slight))
18	M	22	108	78	30	+ 1%	Chr tonsillitis, eyestrain
19	M	22	120	90	30	+ 1%	Chr sinusitis, otitis media
20	F	40	116	80	36	+21%	Hyperthyroidism (mild)
21	F	30	116	80	36	— 1%	Goiter (simple), chr tonsillitis
22	F	39	134	82	52	— 3%	None
23	F	40	118	80	38	—27%	Hypothyroidism, dental abscesses
24	F	56	110	76	34	—13%	Hypothyroidism, cholecystitis
25	F	26	110	76	34	— 9%	Pelvic infection
26	M	17	115	86	29	+ 1%	Goiter (simple), eye-strain
27	F	19	108	78	30	—11%	(Hypothyroidism (post-op), obesity, chr tonsillitis)
28	F	27	115	64	51	— 3%	None
29	F	19	105	70	35	+ 2%	(Goiter (simple), chr tonsillitis, mitral stenosis)
30	F	24	98	74	24	+10%	Hypo-pituitarism, ovarism
31	F	26	130	80	50	0	Chr tonsillitis, pregnancy
32	M	29	126	90	36	+ 5%	None
33	M	55	132	80	52	+ 1%	Achlorhydria, varicocele
34	F	37	102	70	32	—10%	Hypothyroidism, pulmonary t b
35	F	39	124	94	30	+ 7%	(Chr tonsillitis, pyorrhoea, Chr sinusitis)
36	M	22	110	76	34	+10%	Chr tonsillitis, pyorrhoea
37	F	28	120	70	50	+17%	(Hyperthyroidism (mild), dental abscess)
38	F	26	110	80	30	— 1%	(Chr tonsillitis, pyorrhoea, paroxysmal tachycardia)
39	M	33	123	89	34	+18%	Thyrototoxicosis (mild)
40	M	35	120	88	32	+ 8%	Pyorrhoea, chr nephritis
41	F	36	120	84	36	+ 3%	Chr tonsillitis, sinusitis, obesity
42	F	34	126	80	46	— 4%	Chr endocervicitis
43	F	31	122	72	50	—11%	Subthyroidism, subovarism
44	F	45	140	70	70	— 7%	Subthyroidism, chr hepatitis
45	F	28	110	78	32	+ 2%	Eye-strain
46	M	41	124	82	42	+ 6%	Chr tonsillitis
47	F	43	130	84	46	— 9%	Chr tonsillitis, menopause
48	M	51	84	62	22	+ 4%	Dental abscess, myocarditis
49	M	28	140	80	60	+ 4%	None
50	F	20	118	88	30	+ 7%	Chr myocarditis, appendicitis

SUMMARY —Females, 38

Males, 12

Average age 31 1 years

Average pulse pressure 38 7 mm Hg

TABLE NO 2—HYPERTHYROIDISM

CASE	SEX	AGE	SBP	DBP	PULSE METABOLIC		COMPLICATING DISEASES —
					PRESSURE	RATE	
					(all plus)		
1	F	53	140	80	60	36%	Chr myocarditis, nephritis
2	F	25	132	90	42	27%	Chr appendicitis
3	F	23	120	68	52	43%	Chr appendicitis
4	M	34	138	88	50	25%	Chr tonsillitis
5	F	53	118	68	50	22%	Chr tonsillitis, cholecystitis
6	F	56	160	90	70	41%	Oral sepsis, chr myocarditis
7	F	70	170	80	90	47%	Mitr endocarditis, auric, fibril
8	F	27	140	86	54	33%	Chr tonsillitis, appendicitis
9	F	46	156	90	66	37%	Oral sepsis, sec anemia
10	F	32	155	80	75	56%	Chr tonsillitis, perident infection
11	F	58	198	102	96	42%	(Chr tonsillitis, oral sepsis, (art hypertension, card hypertrophy
12	F	42	114	70	34	22%	Rheum arthritis, chr appendicitis
13	F	48	156	78	78	24%	(Chr sinusitis, perident infection, (cholecystitis, appendicitis
14	F	39	120	75	45	72%	Chr tonsillitis, alveolar abscess, (cholecystitis, appendicitis
15	F	35	155	80	75	34%	Chr tonsillitis
16	F	42	170	90	80	21%	Chr tonsillitis, uterine, fibroid
17	F	44	150	68	82	65%	Chr tonsillitis, perident infection
18	M	33	140	66	74	62%	Iodine intolerance
19	F	27	128	80	48	44%	Perident infection, appendicitis
20	F	41	130	88	42	50%	Chr tonsillitis, appendicitis
21	F	23	116	84	32	27%	Chr tonsillitis
22	F	61	164	84	80	22%	Oral sepsis, tonsillitis, cholecyst
23	F	52	174	70	104	91%	Chr myocarditis
24	M	22	158	70	88	39%	Chr tonsillitis, rhinitis
25	F	19	142	78	64	49%	Chr tonsil, sinusitis, appendicitis
26	F	17	132	60	72	45%	Chr tonsillitis
27	F	21	155	86	69	79%	Dental caries
28	F	24	165	60	105	48%	Chr tonsillitis
29	F	24	138	78	60	37%	Pelvic infect, perineal laceration
30	M	42	145	90	55	43%	Chr tonsil, myocard, oral sepsis
31	M	24	150	100	50	30%	Chr tonsil, nephritis, bronchitis
32	F	36	115	80	35	24%	Chr cystitis, pyelitis, oral sepsis
33	M	29	124	60	64	40%	Chr appendicitis
34	F	22	110	74	36	23%	Pylorospasm
35	F	49	152	84	68	68%	Chr cholecystitis, appendicitis
36	M	46	150	100	50	38%	
37	F	39	155	84	71	57%	(Chr tonsil, perident infection, (chr cholecystitis, appendicitis
38	F	37	120	82	38	35%	Chr tonsil, oral sepsis, mitr stenosis
39	M	50	150	80	70	25%	Cardiac hypertrophy
40	F	52	126	70	56	97%	Chr tonsillitis, periartthritis
41	F	28	155	80	75	57%	Chr tonsillitis, pregnancy (early)
42	F	16	136	72	64	42%	None
43	F	42	165	88	77	91%	Chr tonsillitis
44	M	22	158	70	88	40%	Chr tonsillitis, rhinitis
45	M	24	144	74	70	71%	Chr tonsillitis
46	F	56	140	90	50	54%	Chr myocarditis, fibrillation
47	M	23	120	54	66	67%	None
48	F	33	124	70	54	77%	None
49	F	43	170	80	90	81%	None
50	F	24	108	86	22	29%	Peridental abscess

SUMMARY Females, 39  
 Males 11  
 Average age 36.5 years  
 Average pulse pressure 63.7 mm Hg

or above. eight (66.6 per cent) have systolic pressures of 140 mm or above

2 "In the differential diagnosis between exophthalmic goiter and adenoma with hyperthyroidism the presence of hypertension (diastolic) is strong evidence that the hyperthyroidism is due to adenomatous goiter because hypertension (diastolic) is rarely found in patients with exophthalmic goiter"

Of the forty patients charted having either toxic adenoma or exophthalmic goiter, only six have diastolic pressures 90 mm or above, of the six, five are of the adenomatous type

3 "An increased pulse pressure in the absence of hypertension, and associated with an increased pulse rate, without many exceptions indicates an increased circulatory rate which, in turn, signifies an elevated basal metabolic rate. If hypertension is present, however, and especially if marked, a high pulse pressure and rapid heart are not necessarily indicative of an increased circulation rate and increased metabolism"

The pulse rates of our hyperthyroid patients are not shown in the tables, but most had tachycardia. The chart indicates that the general trend of the metabolic rates increases commensurately with the pulse pressures. The number of striking exceptions, however, would render questionable the statement that the metabolic rate, even in the absence of diastolic hypertension, can be predicted from the pulse rate and pulse pressure.

It is realized that the preceding analysis is somewhat irrelevant to the subject of this paper, that the number of patients in each group of hyperthyroidism is too small to justify

definite conclusions, and, finally, in any clinic the accuracy of a classification of hyperthyroid patients, especially those not operated, into the two major groups is open to question.

After the routine examination of the patient is made the patient should be kept under observation. The details of the metabolic test must be explained before it is begun, emphasizing their simplicity, the necessity of co-operation, and the influence of anxiety in contributing to an erroneous rate. Much can be learned by the conscientious and experienced technician while making the tests. Relaxation and co-operation in a psycho-neurotic are ordinarily more difficult to obtain than in a hyperthyroid. Usually, however, in the former the functional features of the patient's behavior become apparent during the test, they are prone to exaggerate the technical difficulties and record weird tracings. A metabolic test giving a rate initially elevated should be repeated each morning until the necessary co-operation is given in a manner satisfactory to the technician and clinician.

Psycho-neurotics when confined within a hospital, separated from their family, friends and daily associations, frequently relax remarkably within a few days. The insomnia, tachycardia and nervous symptoms may magically disappear. Focal infections should be eradicated. If then the point is driven home convincingly to the patient that the thyroid disease has been disproved conclusively, and the real functional nature of the symptoms explained, with helpful suggestions relative to removing the cause of the complaints, the transformation is at times striking.

ing and gratifying Unfortunately, however, even after the diagnosis is reached, the domestic, financial or marital problems cannot be corrected invariably In such cases improvement is problematical

In conclusion, it is admitted that the comparatively simple procedures enumerated will not always remove the veil of uncertainty from the mind of the physician in every case presenting

the diagnostic problem discussed But if this paper will serve to restrain the surgeon from premature subtotal thyroidectomy in the neurotic, and the medical man, or internist, from too quickly consigning a moderate hyperthyroid patient to the unenviable category of a hypochondriac, the effort will not have been fruitless. For of such (victims) is the kingdom of chiropractic and other cults

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# Scurvy in the Presence of Thyrotoxicosis\*

By R H KAMPMEIER, M D , F A C P , *Pueblo, Colo*

A SEARCH of the literature available to me has failed to reveal a case report in which this peculiar association of diseases occurred

The patient whose case is reported below showed a group of symptoms and signs which confused the diagnosis so that, though scurvy was considered at once, the thyrotoxicosis was not appreciated at first

## *Case Report*

*Case Report*—J T, a Spaniard aged 52, barber by occupation, entered the Pueblo Clinic on April 5, 1930, and was referred to me by Dr H A Black.

*Chief Complaint*—Diarrhea, fever, and weakness

*Present Illness*—In December, 1929, the patient had had a routine physical examination and was apparently well. In January, 1930, he had a severe "cold", since which time he had had a persistent cough, which was non-productive.

From the onset of the illness in January there had been a persistent, gradual loss of weight. The appetite was good until about two weeks before admission, when it became very poor. The weight before the illness had been 119 pounds, the patient stated he had lost about 30 pounds in weight.

Some weeks after the onset of the illness a diarrhea developed, so that six or seven watery stools were passed daily. The stools contained mucus, but no blood, and only slight abdominal pain occurred at times. He

was greatly troubled with flatus. Because of the diarrhea, though the appetite was good, he limited his food to bread, toast, milk, tea, coffee, cereals, and at times eggs. He ate practically no fresh meat, except very occasionally, and fresh fruits and vegetables were used only at rare intervals and these, he said, passed through the bowel unchanged. Thirst had been marked from the onset.

Sweats appeared some weeks before admission to the clinic, and fever had been found by a physician who had seen him previously and, because of this and the cough, had considered pulmonary tuberculosis.

The patient had noted "spots" on the feet and legs on the day before admission.

*Past History*—This was essentially negative.

*Family History*—Wife and one child were alive and well.

*Physical Examination*—The patient was a white male, of short stature and very emaciated. Weight was 90 pounds.

The head was negative. There was exophthalmos, which the patient said was present all his life. There was no lid lag, and no abnormality in wrinkling of forehead nor in convergence. Pupillary reflexes were normal. There was no apparent abnormality of the extra-ocular muscles. The conjunctivae were pale.

The tonsils were atrophic, and the pharynx appeared granular and red. The gums showed a marked degree of retraction and were spongy, with an advanced pyorrhea. In the neck the thyroid was palpable in both lobes, though there was no real enlargement.

There was a generalized lymphadenopathy. The nodes of the right posterior cervical

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\*From the Pueblo Clinic, Pueblo, Colo

chain were 2-3 cm in length and about 0.5 cm in diameter. In the right anterior chain there were also several enlarged nodes. In both chains in the left neck were glands varying in size from a pea to one or more centimeters in diameter. Enlarged nodes were palpable in each axilla, up to the size of an almond. Both epitrochlear glands were about 1 cm in diameter. The inguinal nodes were larger than average. All enlarged lymph nodes were freely movable, those in the right neck were quite firm and slightly tender.

The chest was of the asthenic type, somewhat emphysematous. Cardiac point of maximum impulse was 8 cm from mid-line. The rate was 108 per minute, no murmurs were heard, but there were numerous extrasystoles. Expansion of the lungs was limited, the percussion note was hyperresonant, no abnormal breath sounds or râles were heard.

The liver edge was palpable. Genitalia were negative. There was some pitting edema over the ankles. The deep reflexes were normal. There was tremor of the fingers.

The skin was interesting for several reasons. The complexion was sallow. Over the wrists and dorsum of the hands was an orange colored discoloration, which had been present for years according to the patient. Over the dorsum of the feet and the lower half of the leg were copper colored areas about 0.5 cm in diameter. Of greatest interest was a diffuse, fine petechial rash involving the dorsum of the foot, the whole leg and lower third of the thighs. The petechial spots were at the site of the hair follicles.

*Technical Examinations* — Urinalysis showed specific gravity of 1.020, a trace of albumin and rare hyaline and granular casts. (Subsequently, after improvement, a concentration test showed nothing remarkable, the albumin and casts having disappeared.) Blood examination showed the following: hemoglobin 70%, red cells 4,300,000, white cells 12,800, with a differential of polymorphonuclears 89%, lymphocytes 9%, endothelial cells 2%. Arneth-Schilling count showed 20 young cells. Coagulation time

was two minutes (capillary tube) and platelets appeared normal on smear.

The blood Wassermann and Kahn tests were negative.

Roentgenologic examination of the chest demonstrated no disease of the lungs. Shadows appearing as if those of enlarged hilus glands were present.

Temperature upon first examination was 100.4 degrees.

*Clinical Course* — The patient entered the hospital two days after the above data were collected. The symptoms had all persisted. The petechial rash had become more aggravated in intensity and distribution, and a scattering of petechiae had appeared upon the flexor surface of both arms in the elbow region. During the first four days in the hospital the temperature fluctuated daily from 99 to as high as 102 degrees. The diarrhea persisted the first three or four days.

A gland was removed from the right cervical region for biopsy. This was reported by the pathologist as showing merely a lymphadenitis.

Immediately upon hospitalization the patient was placed on a high vitamin diet, specifically receiving the juice of four to six oranges a day. The appetite improved at once, the diarrhea ceased and the temperature reached normal by the fourth day. No new petechiae appeared and those present faded rapidly in the first three days. The edema of the legs cleared.

The general improvement continued, though the pulse rate remained somewhat elevated and the complaint of weakness did not improve. About two weeks after improvement began a basal metabolic determination showed +47% which was checked two days later with the result of +36%.

Thyroidectomy was refused. After being absent from town for a time, the patient presented himself again three months after he was first seen. He had gained a total of 14 pounds. The pulse rate was still 120 per minute, there was tremor of the fingers. The size and character of the lymph nodes had not changed. The appetite had remained good and there had been no recurrence of diarrhea, fever, or petechial rash.

## COMMENT

The numerous symptoms and signs which presented themselves upon the patient's admission made an immediate diagnosis impossible

A provisional working diagnosis of lymphatic leukemia was made, trying to thus explain most of the presenting symptoms and signs under one disease picture. Thus asthenia, loss of weight, anorexia, fever, tachycardia, generalized lymphadenopathy and purpuric rash could be grouped to make up such a syndrome

However, being struck by the petechial rash of the hair follicles as I had seen it in other cases of adult scurvy, I made a note to this effect, not accounting for the lymphadenopathy in this manner

Leukemia was ruled out by the blood picture and biopsy revealed only a lymphadenitis, the serology was negative. The diarrhea, fever, anorexia and petechial rash responded at once to the administration of orange juice. It was only then that the thyrotoxicosis was recognized

I believe this to have been an unquestionable case of scurvy in a patient with thyrotoxicosis. In some years of constant contact with large numbers of patients with thyrotoxicosis, I have never before seen scurvy as a complication. Not infrequently diarrhea accompanies thyroid toxicity, and this coupled with the inadequate diet of this patient undoubtedly accounts for the deficiency in vitamin C with the resultant occurrence of scurvy



# Editorial

## STATUS

### THYMICO-LYMPHATICUS

Among the intrinsic pathological constitutions there is none possessed of more definite anatomical stigmata than those of *status thymicolymphaticus*. From medical antiquity the conception of lymphatism, or *status lymphaticus*, as a morphological-physiological type possessed of certain definite attributes, chiefly exudative, has been generally accepted. The frequent, almost constant, participation of the thymus in the morphological complex of this constitution has led to its more precise designation. The external bodily configuration found in *status thymico-lymphaticus* is far from constant. In childhood, those belonging to this constitution usually appear well nourished, the skin is soft and fine in texture, but pale, and a certain roundness of configuration, particularly of thorax and thighs is usually present. In more advanced years examples of this condition are found among well muscled brachymorphs with square frames, and very frequently, also, in asthenic dolichomorphs with slender long bones. In boys and young adult males there may be a certain femininity in bodily configuration and in distribution of body hair. When the bodies of those belonging to this constitution are examined at autopsy certain anatomical variations from the normal are found with great uniformity. The

thymus is hyperplastic or unduly persistent, or both hyperplastic and persistent. The hyperplasia involves both cortex and medulla, but especially the latter, and in the adult may be revealed chiefly by the large size of the thymic adipose tissue which has incompletely replaced the thymus although maintaining the form of the organ, throughout which small lymphoid islands with corpuscles of Hassall are distributed. Thus it comes about that a very frequent pathologic diagnosis in our records is that of fatty atrophy of a persistent hyperplastic thymus. There is also a general lymphoid hyperplasia which is noted particularly in respect to the tonsillar ring, the solitary and agminated lymphoid nodules of the gastro-intestinal tract, the mesenteric and retroperitoneal lymph nodes and the spleen. In the latter, particularly, the large germinal centers of the follicles may show a high degree of lymphoid exhaustion, particularly if some infection or intoxication has called for a marked production of lymphocytes. Equally constant are the changes in two other systems. The adrenals are hypoplastic, especially in respect to the chromaffinic tissue, and the cardio-vascular system is also hypoplastic. So surely do these changes occur in mutual association in the thymico-lymphatic constitution that the prosector in a demonstration autopsy can predict with assurance the pathol-

ogical state of heart, aorta and adrenals when he lifts the sternum and views the enlarged or persistent thymus. It is with considerable surprise, therefore, that we find that Young and Turnbull (An Analysis of the Data Collected by the Status Lymphaticus Committee, The Journal of Pathology and Bacteriology, 1931, xxxiv, (March), 213-258), in a study conducted along modern statistical lines, reach conclusions considerably at variance with those just expressed. For instance, they state that an abnormally large thymus *in itself* cannot be considered to be indicative of "status thymico-lymphaticus" when no obvious cause of death is found post-mortem. Likewise they found little, if any, association between the weight of the thymus and the amount of lymphoid tissue in the various parts of the body, and no definite evidence of any concomitant general hyperplasia of lymphoid structures in the cases with an abnormally large thymus. In their material there was no evidence of an association between arterial hypoplasia and an abnormally large thymus. However, they are in agreement with the generally accepted opinion that in exophthalmic goiter (Graves' constitution) the average gross weight of the thymus is distinctly above the normal. Since the investigation upon which these conclusions were based was conducted in a thorough and painstaking manner and the data analyzed by approved statistical methods it is of interest to discover why there should be such variance from the accumulated opinion of many presectors who have done thousands of autopsies but whose beliefs were founded on impressions

and not upon weighted mathematical data. The answer is not hard to find. The special objects of the investigation undertaken by this Committee were to establish by means of a large series of weights and measurements the standards of weight for age, and proportion to body weight, of the normal thymus at all ages, and to investigate closely the precise cause of death in persons dying suddenly from unexplained or trivial causes where the only apparent abnormality was the presence of a large thymus. In pursuance of these objects, record cards were prepared calling for appropriate information. It is significant as showing a lack of appreciation of the constitutional pathology involved that these cards did not call for information about either the adrenals or the aorta. Of these cards 680 were available for analysis and, from these, 464 cases of which 279 were under 16 years of age, were selected as constituting a *normal* group from which the mean weight and variability of the thymus at different ages was to be determined. The weights and measures were recorded by a number of observers and there is no certainty that in each instance other mediastinal structures and particularly the pericardium were equally well dissected from the thymus before weighing. This is an extremely important point in respect to an organ as small as the thymus. To this "normal" group there were admitted cases, among others, in which death was due to trauma from accidents, firearms or burns, to hemorrhage at surgical operations; to poisoning by gas or inorganic or organic chemicals; to asphyxia during or after delivery, in infantile con-

vulsions or epileptic fits, and to anesthetics or operative shock. Many of these are precisely the conditions in which the thymico-lymphatic constitution might turn the scale to a fatal issue. Among the presumably "normal" cases, in the age group 1 to 6 years there appeared three thymuses of such unusual size (99.2, 84 and 70 grams) that the authors omitted them in computing the mean values for the group. This alone shows the intrinsic weakness of the fundamental data. It is not surprising, then, that values greater than those of other similar investigations and distinctly higher than those usually considered normal were obtained. The high values for standard deviations in each sub-group show how heterogeneous the supposed normal group was. For instance in the full-term fetuses the mean weight of the thymus was  $21.83 \pm 1.55$  grams and the standard deviation,  $12.78 \pm 1.09$ ; in age group 1-6 years, mean weight,  $23.30 \pm 0.86$  grams, with standard deviation,  $10.36 \pm 0.61$ ; 11-16 years, mean weight  $33.91 \pm 1.33$  grams, standard deviation,  $14.62 \pm 0.94$ . These means are from one and one-half to three times greater than those considered normal in the autopsy material under the supervision of the writer. It is our belief that any thymus exceeding 20 grams in weight is of pathological significance. Young and Turnbull recognized the difficulty with their normal material for they found that in ten instances the gross weight of the thymus exceeded the mean weight in the corresponding age-group by at least twice the standard deviation or variability. Since such a deviation is likely to occur fortuit-

ously in approximately but 1 in 50 trials, they felt that all of these thymuses might properly be deemed to be abnormal in size. We can have but the greatest admiration for the extended mathematical analysis of the data collected by this Committee and full appreciation of the labor involved in their analysis, but it must always be borne in mind that the conclusions derived from a statistical study are no stronger than the original unit data upon which they are based. Much more rigid criteria must be set up and the full implication of the thymico-lymphatic constitution considered in selecting a group to serve as "normals" for the basic material of such an investigation.

#### THE TERCENTENARY OF CINCHONA

It is now about three hundred years since Cinchona bark was first made use of by Europeans. There is much evidence to show that the Indians of Peru were aware of its curative value before the arrival of the Jesuit missionaries, but the usual statement in regard to the first utilization of the bark by Europeans is the one which led to the application of the name *Cinchona* by Linnaeus. Having been appointed Viceroy of Peru in 1628, the Count of Chinchon went with his Countess to that country to take up his official duties. There they both suffered from fever and, in 1638, Don Juan de Vega, physician to the Viceroy, cured the Countess by administration of the bark at Lima. This event is depicted in three frescos in the Hospital de Santo Spirito in Rome, and through it and the early transportation of the bark to

Europe by the Jesuit fathers, the remedy was known for many years as Countess's Powder, Jesuit's Powder, and Cardinal's Powder. Henry S Wellcome states decisively, however, in his foreword to the Souvenir of the Cinchona Tercentenary Celebration and Exhibition held at the Wellcome Historical Medical Museum during the past few months, that the tercentennial year should be 1930 and not 1938. He dates the first utilization of Cin-

chona in the treatment of an European to the former year, when Don Juan Lopez de Canizares, the Spanish corregidor of Loxa, was cured of intermittent fever by an Indian cacique who taught him the curative attributes of the bark and the method of administering it. Thus, although quinine was not isolated until 1820, Cinchona has now entered upon its fourth century of usefulness since it was first made known to our civilization.



SYDNEY R. MILLER, B.S., M.D., Baltimore, Maryland  
Retiring President

SYDNEY R. MILLER, B S , M D , Baltimore, Maryland

Retiring President

AMERICAN COLLEGE OF PHYSICIANS

Born, 1884, B S , New York University, M D , Johns Hopkins University School of Medicine, 1910, Director of Laboratories, Phipps Psychiatric Clinic, 1912-14, Associate Clinical Medicine, Johns Hopkins University School of Medicine, 1910 to date, Assistant Professor of Medicine, University of Maryland School of Medicine, 1922 to date, Assistant Attending Physician, Johns Hopkins Hospital, Attending Physician and Member of Executive Committee, Union Memorial Hospital, Member, Zeta Psi, Alpha Omega Alpha, Phi Beta Kappa Fraternities, Member of the Baltimore Medical Society, Maryland State Medical Society, American Medical Association, Southern Medical Association, American Climatological and Clinical Association, Inter-urban Clinical Club, and a Fellow of the American College of Physicians since 1920. He is a life member of the College.

His Presidency of the American College of Physicians was marked by enthusiasm, foresight, energy and untiring effort in behalf of the College. Due chiefly to him the Baltimore Clinical Week was one of the most successful the College has ever held.



S. MARK WHITE, B.S., M.D., Minneapolis, Minnesota  
Newly Inducted President, 1931-32

S MARX WHITE, B S , M D , Minneapolis, Minnesota

Newly Inducted President, 1931-32

AMERICAN COLLEGE OF PHYSICIANS

Born, 1873, B S , University of Illinois, M D , Northwestern University Medical School, 1897, Post-graduate work at the University of Vienna and the University College Hospital of London, Demonstrator, Pathology and Bacteriology, University of Minnesota Medical School, 1898-00, Assistant Professor of Medicine at same institution, 1900-08, Associate Professor of Medicine at same institution, 1908-19, Professor of Medicine at same institution, 1900 to date, Member of Staff, Northwestern Hospital, 1908 to date, St Mary's Hospital, 1919 to date, Abbott Hospital, 1921 to date, Eitel Hospital, 1926 to date, Member and ex-President of the Minnesota State Board of Health, Member, Nu Sigma Nu, Alpha Omega Alpha and Sigma Xi Fraternities, Member of the Hennepin County Medical Society, Minnesota State Medical Association, American Medical Association, Minnesota Academy of Medicine, Minnesota Pathological Society, Interurban Clinical Club, Association of American Physicians and a Fellow of the American College of Physicians since 1922

Dr White has been an active Fellow of the College from the beginning of his membership. He has been a member of the Board of Regents and a member of the Committee on Credentials for several years, a Vice President and the General Chairman of its Fourteenth Annual Clinical Session. Under Dr White's able generalship the Minneapolis meeting in 1930 stands out as one of the most successful of the College.





FRANCIS MARION POTTINGER, Ph B, Ph M, A M, M D, LL D,  
Monrovia, California  
President-Elect, 1931-32

FRANCIS MARION POTTENGER, Ph B , Ph M , A M , M D , LL D ,  
Monrovia, California  
President-Elect, 1931-32  
AMERICAN COLLEGE OF PHYSICIANS

Born, 1869, Ph B , Ph M , A M , LL D , Otterbein College, Westerville, Ohio, M D . Cincinnati College of Medicine and Surgery, 1894 Postgraduate study at New York Polyclinic and European Clinics, including Vienna, Berlin and London Lecturer on Diseases of the Chest and Climatology, University of Southern California College of Medicine, 1903-04, Professor of Clinical Medicine, same, 1905-09, Professor of Diseases of the Chest, College of Physicians and Surgeons of the University of Southern California, 1914-20, President and Medical Director, The Pottenger Sanatorium, Member, Board of Trustees, Otterbein College; Member, Phi Rho Sigma and Pi Gamma Mu Fraternities, Member and ex-President, Los Angeles County Medical Association, Member and ex-President, Los Angeles Clinical and Pathological Society, Member and ex-President, Southern California Medical Society, Member, California Medical Association, Member, Pacific Interurban Clinical Club, Member, California Academy of Medicine, Member, Trudeau Society of Los Angeles, Fellow, American Medical Association, Member and ex-President, the American Therapeutic Society, Secretary, Association for the Study of Internal Secretions, Member, American Climatological and Clinical Association, Member, American Association for the Study of Allergy, Member, American Public Health Association, Member and ex-President, American Sanatorium Association, Member, American Heart Association, Member, Director and Vice President, Los Angeles Tuberculosis Association, Member National and International Association for the Study and Prevention of Tuberculosis, Member, Eugenics Society of the United States of America, Member, Association for the Advancement of Science, Member, Science League of America, Member, National Geographic Society, Member and Regent, Pacific Geographic Society, Member, American Academy of Political and Social Science, and a Fellow of the American College of Physicians since 1916 He is a Life Member of the College

Dr Pottenger has been a most productive writer, being the author of at least eight volumes dealing with various phases of tuberculosis Several of his books have been published in from two to four editions Of especial importance is his work on the vegetative nervous system and symptoms of visceral disease, now in the second edition

Dr Pottenger became a Fellow of the American College of Physicians almost at the beginning of its organization Few members have as intimate a knowledge of the development of the College as he He has been a member of the Board of Regents since 1923, and Vice President, 1929-30 Though far removed from the place of meetings of the College and its Board of Regents, he has been most regular in attendance through all these years, and has always held the welfare of the College foremost in his endeavors

## Abstracts

*The Behavior of Lead in the Animal Organism, II Tetraethyl Lead* By ROBERT A. KEROE and FREDERICK THAMANN. (The American Journal of Hygiene, March, 1931, p 478)

Because of its peculiar physical properties which promote a different type of initial distribution in the tissues when it is absorbed as compared to the water-soluble compounds of lead, tetraethyl lead offers an especially interesting field for investigation. Its high selective affinity for fat-containing tissues and for the nervous system has been known for some time. Its wide distribution in a low concentration in motor fuels has raised the question whether there is absorption of lead through the skin of persons who come in contact with such gasoline, and whether lead thus absorbed may be expected to accumulate in nervous and other lipoid-containing tissues. Using rabbits in carefully controlled experiments, the authors found that tetraethyl lead is absorbed through the intact skin, but that this absorption is inappreciable when in excess of 0.1 per cent. The initial distribution of the lead in the tissues in rapid tetraethyl lead absorption corresponds to that of an oil-soluble material and indicates that some portion of the tetraethyl lead is absorbed and circulates as such. However, tetraethyl lead is rapidly decomposed by the tissues so that, after a period of from three to fourteen days, all of the lead is distributed in a manner characteristic of water-soluble lead compounds, and excretion follows quantitatively that of water-soluble lead compounds. From this evidence, it is concluded that tetraethyl lead poisoning is not different from lead poisoning occasioned by other compounds of lead.

*Miliary Lung Disease Due to Unknown Cause* By R. R. SAYERS and F. V. 1482

MERIWETHER (Public Health Reports, Vol 45, No 49, December 5, 1930, p 2994)

Of 18,285 individuals examined in connection with a systematic investigation for the study and control of silicosis and tuberculosis among miners, about 125 instances were found in which the roentgenograms appeared to be those of miliary tuberculosis, but the patients were, with two exceptions, apparently healthy. The cases ranged in age from 16 to 69 years. With one exception, an Indian, the subjects were all white, native-born Americans, most of whom came from rural districts or had worked in the harvest fields. Eight per cent had never worked in or around mines. Many of the subjects (65.6 per cent) gave no symptoms. Certain of the remainder had had cough, dyspnea, expectoration, hemoptysis (blood-tinged mucus), loss of strength, loss of appetite, night sweats, fatigue or pain in the chest. Upon X-ray examination, a decided enlargement of the hilum shadows was found in 91.2 per cent of the group. The most characteristic finding was the large number of discrete, dense, shotlike spots scattered over the lungs, in numbers ranging from less than 25 to more than 500 in each patient. In 94 per cent of the cases more than half of the spots were located in the bases, while in the other 6 per cent they were scattered about equally over the lung area. Two cases only showed tubercle bacilli in the sputum. Unstained smears of 31 cases (all those examined) were positive for higher fungi, two types of which were identified, *Aspergillus fumigatus* fisheri and *Aspergillus niger*. Ten cases tested with antigen of the former gave negative reactions, of 6 cases tested with *Aspergillus niger* all gave positive results. Miliary tuberculosis, pneumoconiosis and calcium metastasis must be considered in differential diagnosis, to-

gether with pneumomycosis. The "miliary calcification of the lungs" reported by Sutherland is probably the same condition as that described here. These miliary calcifications may be due primarily to fungus infection.

*Acute Mercury Poisoning. Report of Twenty-one Cases with Suggestions for Treatment.* By B. I. JOHNSTONE. (The Canadian Medical Association Journal, April, 1931, p. 500.)

The main details in respect to 21 patients treated in the Henry Ford Hospital, Detroit, for acute mercury poisoning are outlined in this article. In 18 of the 21 cases, the bichloride was the compound responsible. The average age of the group was 30.8 years, and there were twice as many women as men. In four, poisoning was definitely accidental, six admitted having taken the drug with suicidal intent, and in the remainder definite information was not obtainable. In two cases, both fatal, poisoning was due to the use of bichloride solution as a vaginal douche. Vomiting occurred in 17 of the 21 cases. It began in from two minutes to one-half hour after ingestion and became frequent and distressing if large amounts of mercury had been taken. The vomitus was often blood stained. All patients showing evidence of toxicity had diarrhoea, beginning within a few hours, with liquid, bulky, extremely fetid, and later bloody, stools. There was marked tenesmus and the whole abdomen became tender, especially so along the course of the colon. By the third day salivation, stomatitis, glossitis, and gingivitis occurred. Oliguria was present in 6 patients and anuria in 2. When considerable absorption of mercury had taken place there was a rapid rise in the non-protein nitrogen of the blood, definitely established by the third day and reaching its maximum by the fourteenth day if the patient still survived. The highest figures were obtained in a patient who died 12 days after a single bichloride vaginal douche: non-protein nitrogen, 293 mg., urea-nitrogen, 240 mg., uric acid, 183 mg. per cent. In treatment, efforts should be directed chiefly towards prevention of absorption, for once the drug has reached the circula-

tion there is no effective antidote in spite of the long list of remedies proposed. In addition to the usual methods it is suggested that after gastric lavage a duodenal tube be passed and transduodenal irrigation carried out with warm saturated solution of sodium bicarbonate. By this method the whole intestine is washed out, removing that portion of the drug which has left the stomach. Gastric lavage and transduodenal irrigation at least once daily for several days thereafter will prevent reabsorption of at least a part of the mercury excreted. Using an ounce of a saturated solution of magnesium sulphate as a stimulant, biliary drainage was done for several hours on a number of patients in the hope of still further reducing reabsorption following excretion from the liver.

*Changes in the Blood Sugar and Blood Phosphorus in Rabbits Following the Injection of Suspensions of Bact. Aertrycke.* By M. E. DELAFIELD. (The Journal of Pathology and Bacteriology, March, 1931, p. 177.)

As there is already experimental and clinical evidence that significant changes in the blood sugar occur in various infections it was thought to be worth while to discover whether changes in blood phosphorus are associated with the bacterial hyperglycemias and hypoglycemias. Suspensions of *Bact. aertrycke* and bacterial filtrates were injected intravenously into rabbits and blood sugar and phosphorus determinations made at frequent intervals. It was found that a hyperglycemia was first produced and that this was followed by hypoglycemia. When death occurred, it was in the hypoglycemic phase. Inorganic blood phosphorus was lessened in amount during hyperglycemia and increased again, often above the initial value, during the hypoglycemic phase. Organic acid-soluble blood phosphorus, on the other hand, in many cases increased during hyperglycemia and decreased during hypoglycemia. These changes in the sugar and phosphorus values are specific in the sense that they are entirely different from the results obtained by the intravenous injection of diphtheria toxin.

# Reviews

*Recent Advances in Biochemistry* By JOHN PRYDE, B Sc (St And), M Sc (Wales), Lecturer in Physiological Chemistry, Welsh National School of Medicine, University of Wales Third edition, with 42 illustrations F Blakiston's Son and Co, Philadelphia, 1931 Price, \$3 50 net

In this edition there has been an extensive revision of the original subject matter and two new chapters have been added, one on "Protein Structure and Proteolytic Enzymes" and the other on the "Cholane Series," which includes the bile acids and sterols. On the other hand the chapters on "Colloids and the Physical Chemistry of Proteins" and on "Chemotherapy" have been omitted. The last-mentioned topic is now considered in another volume in the *Recent Advances* series, "Recent Advances in Chemotherapy" by Dr W G M Findlay. The volume under review covers a diverse selection of the more important recent advances in biochemistry, in particular those which serve to indicate the trend of present day research in this field. The main topics presented, in addition to the two previously mentioned, are Amino Acids and Urea Formation, Sulphur Compounds and Protein Metabolism, The Role of Tyrosinase, The Nucleo-Proteins, The Carbohydrates, The Biochemistry of the Fats, The Biochemistry of Phosphorus Compounds, The Vitamins, Haemoglobin and Related Natural Pigments, The Chemical Basis of Specific Immunological Reactions. Each chapter is followed by selected references to the sources of the new material presented. The style of this book is excellent and the free use of structural formulas and of diagrams makes for clear exposition. It can be recommended particularly to students who wish to supplement the material of the older textbooks and to those working in related fields such as Internal Medicine, Physiology and Pathology, who need to keep themselves informed upon the newer viewpoints in Biochemistry.

*Calcium Metabolism and Calcium Therapy* By ABRAHAM CANTAROW, M D, Assistant Demonstrator of Medicine in the Jefferson Medical College, Philadelphia, 215 pages Lea and Febiger, Philadelphia, 1931 Price \$2 50 net

This monograph presents in a logical manner the present state of knowledge in respect to calcium metabolism. Although there is much that is still the subject of controversy in this field, the author has succeeded in giving a clear exposition of his subject matter, considering first the normal metabolism of calcium, then calcium metabolism as altered by disease, and finally, the therapeutic uses of calcium. Under each of these main divisions there are appropriate subdivisions covering the entire field of laboratory and clinical research germane to the subject. Such a treatise will doubtless require frequent revision, but its importance cannot be overestimated for, as the author states in the preface, "calcium metabolism occupies a position in current medical literature and thought comparable to that held by carbohydrate metabolism some years ago." While it is to be expected that parathyroid hormone, ultra-violet irradiation and vitamin D would receive full discussion, the inclusion of the less discussed therapeutic uses of calcium, such as in lead poisoning, is evidence of the completeness of the treatment of the subject. This book will be very useful to the practitioner who desires scientific guidance as to when and how calcium should, or should not, be used in the treatment of disease.

*Epidemiological Essays* B F G CROOKSHANK, M D, F R C P The MacMillan Company, New York, 1931 Pages x + 136 Price \$2 50

As the author shrewdly predicts in his prefatory note, the reviewer finds in this volume a collection of papers, all of which have appeared previously. Some of them had their first appearance more than ten

years ago and much that is of value has been added to the subjects discussed during those years. This is especially true of Acrodynia, which is brought up only to 1920, of Botulism and of Encephalitis Lethargica. Thus it is that if the reader judges these essays by their scientific content he is sure to be disappointed. Their value lies rather in the emphasis put upon the Hippocratic Epidemiology, in contrast to the modern statistical method of treating this subject, in interesting contributions to the History of Medicine, and in certain common-sense observations upon the foibles of therapeutic faddists who overlook the fundamentals of medical practice.

*Intestinal Toxemia Biologically Considered*

By ANTHONY BASSLER, M.D., F.A.C.P.  
With 16 text illustrations. F. A. Davis Company, Philadelphia, 1930. Pages xvi + 433. Price \$6.00 net.

This book develops more completely the author's theory and practice in regard to the biological aspects of intestinal toxemia, and is a fuller statement of the technical procedures involved, than was possible in his earlier texts. It represents, also, a fuller experience, covering therapeutic results in 5000 cases. The author pays his respects in no uncertain terms to the procession of fads which have been vaunted as cures for intestinal toxemia, such as colonic irrigations, Bulgarian bacilli, *Bacillus acidophilus*, purgations, mineral oil and now the ingestion of yeast. In place of these he advocates identification of the intestinal flora and the rectal or sub-cutaneous injection of vaccines and ectoantigens, of which he lists no less than 109 and 76 respectively. Much of the book deals, therefore, with bacteriological methods and four large folding tables are employed to present this data. The conclusions are those of an enthusiast and for the greater part are presented without supporting evidence. Few readers will be willing to accept as facts such assertions as that the in-

testine is the source of the original infection in the vast majority of all cases of both acute and chronic endocarditis, that practically every case of chronic myocarditis is a neglected case of intestinal toxemia, or that more chronically infected tonsils occur from the intestine than from the pharyngeal surface. It is unfortunate that such a well-printed book should have illustrations that are as inferior as the group reproducing photomicrographs of intestinal pathology. These might easily be improved and many loosely written sentences should be recast if a second edition appears.

*Potter's Therapeutics, Materia Medica and Pharmacy.* The Special Therapeutics of Diseases and Symptoms, the Physiological and Therapeutical Actions of Drugs, the Modern Materia Medica, Official and Practical Pharmacy, Prescription Writing, and Antidotal and Antagonistic Treatment of Poisoning. By SAM'L. O. L. POTTER, A.M., M.D., M.R.C.P. Lond., Fifteenth Edition, revised by R. J. E. SCOTT, M.A., B.C.L., M.D., xv + 997 pages. P. Blakiston's Son & Co., Philadelphia, 1931. Price in cloth, \$8.50.

The fifteenth edition of this well-known reference book follows the general plan of those which preceded it. Much new material has been added and certain sections which had become obsolete have been deleted. It is intended to be a compendium of concise information regarding both official and non-official drugs and preparations, and this expectation is met in a most satisfactory manner. For busy physicians, particularly those who through choice or necessity do their own dispensing, and for pharmacists, this work will continue to be of great value. The alphabetical arrangement, thumb index to major divisions, conveniently placed tables and an unusually complete index increase its usefulness and make its subject matter readily available.

# College News Notes

## THE AMERICAN COLLEGE OF PHYSICIANS

### FINANCIAL STATEMENTS

FOR 1930

Summarizing the Financial Reports, it may be stated that gross income for the year ending December 31, 1930, amounted to \$74,834 59 (1929—\$68,946 83), and that the net expenditures amounted to \$51,619 80 (1929—\$47,584 44), leaving a balance of \$23,214 79 (1929—\$21,362 39), \$3,100 (1929—\$1,200) of which is added to the Endowment Fund and \$20,114 79 (1929—\$20,162 39) added to the Principal of the General Fund. During the year, the Endowment Fund, made up of Life Membership subscriptions, was increased from \$5,300 to \$8,400, and the General Fund increased from \$60,624 07 to \$80,738 86, making the total assets of the College as of December 31, 1930, \$88,338 86 (1929—\$65,924 07)

The cost of conducting the Minneapolis Clinical Session was \$11,320 23, which was reduced through profits on the Commercial Exhibits and guest fees by \$7,946 90, or a net of \$3,373 33 (Boston, 1929—\$3,664 93)

The Annals of Internal Medicine for the calendar year showed a gross cost of \$19,754 65 and a gross income of \$19,155 00, or a net deficit of \$599 65. This deficit would be eliminated if a reasonable valuation were placed on the surplus stock. The net advertising profit on the Journal was \$3,543 49, as compared with \$2,263 46 for 1929. Actually Volume III, completed with the June, 1930, issue, showed a surplus of \$561.19, the first time in the history of the Journal that a credit balance had ever been shown—and thus, too, after the Journal has been constantly improved and enlarged.

It should be pointed out that the amount of traveling expenses not only on the account of the Annual Clinical Session, but also on the account of the Executive Secretary's Office, includes the traveling expenses of the Officers and Regents to the meetings officially called for the Board of Regents.

In addition to \$43,036 70 (1929—\$26,820 60) invested in securities (see Schedule No. I), \$22,523 20 is carried in Savings Accounts and \$20,654 00 is in Checking Accounts (per complete statements filed by the Auditor)

Clement R. Jones, Treasurer  
E. R. Loveland, Executive Secretary

## AMERICAN COLLEGE OF PHYSICIANS, INC

Balance Sheet, December 31, 1930

## ASSETS

Cash in Bank and on Hand		\$43,277 20	
Bonds Owned (Schedule No I)		43,036 70	
Accrued Interest on Bonds		302 92	
Inventory of Keys, Pledges, Frames, etc		493 45	
		<u>\$87,110 27</u>	
Deferred Expenses for the Fifteenth Annual Clinical Session (Paid in Advance of 1931)		377 07	
Furniture and Equipment	\$3,227 80		
Less, Allowance for Depreciation	<u>291 78</u>	<u>2,306 02</u>	\$89,793 36

## LIABILITIES

Deposits by Candidates, Applications Pending		30 00	
Deferred Income			
Fifteenth Annual Clinical Session			
Advance Collections for Exhibits	\$ 602 46		
Annals of Internal Medicine			
Advance Subscriptions, Volume V	806 34		
Advance Subscriptions, Volume VI	<u>15 70</u>	<u>1,424 50</u>	<u>1,454 50</u>
Excess of Assets over Liabilities			<u>\$88,338 86</u>

## FUNDS

Endowment Fund (See Schedule No II)	\$ 8,400 00	
General Fund (See Schedule No III)	<u>79,938 86</u>	<u>\$88,338 86</u>

## SCHEDULE No I

## INVESTMENTS

December 31, 1930

Par Value	Bonds	Cost
3,000	Borough of Steelton, Pa, 4½s, 1933	\$ 3,071 25
5,000	Canadian National Railway 5s, 1969	4,987 50
2,000	Canadian National Railway 5s, 1969	2,055 00
2,000	Canadian National SS Co 5s, 1955	2,040 00
2,000	City of Detroit 4¾s, 1944	2,010 40
2,000	City of Houston 4¾s, 1942	2,077 50
1,000	City of Montreal 5s, 1956	1,071 30
2,000	City of Newark 4½s, 1944	2,075 00
10,000	City of Philadelphia 4½s, 1979	10,225 00
2,000	City of Toronto 5s, 1936	2,020 00
500	Oklahoma Gas & Electric Co 6s, 1940	487 50
2,000	Province of Alberta 4½s, 1956	1,896 00
5,000	Province of Ontario 4½s, 1933	4,925 79
1,000	Province of Ontario 5s, 1942	1,052 26
2,000	Port of New York Authority 4½s, 1952	2,042 20
1,000	Township of Cheltenham 4¾s, 1943	1,000 00
<u>\$42,500</u>	Total Annual Yield 4 6%	<u>\$43,036 70</u>



## SCHEDULE No II

## ENDOWMENT FUND, PRINCIPAL

For the year ended December 31, 1930

Balance, January 1, 1930	\$5,300 00
Life Membership Fees Collected During the Year Ended December 31, 1930	3,100 00
Balance, December 31, 1930	<u>\$8,400 00</u>

## SCHEDULE No III

## GENERAL FUND, PRINCIPAL

For the year ended December 31, 1930

Balance, January 1, 1930	\$60,624 07	
Less, Transfer to Endowment Fund of Initiation Fees of Life Members paid prior to January 1, 1930	<u>800 00</u>	\$59,824 07
Add, Net Income for the Year Ended December 31, 1930 (Schedule No IV)		<u>20,114 79</u>
		<u>\$79,938 86</u>

## SCHEDULE No IV

## GENERAL FUND, INCOME AND EXPENSES

For the Year ended December 31, 1930

## INCOME

Annual Dues	\$24,698 80	
Initiation Fees	16,580 00	
Interest on Bank Deposits	1,461 06	
Income from Bonds Owned	1,218 18	
Income from Endowment Fund	411 00	
Profit from Sale of Keys, Pledges, Frames, Etc	242 30	
Receipts from 1929-30 Directory	10 05	
Receipts from Annals of Clinical Medicine	<u>11 30</u>	
Total Income		\$44,632 69

## EXPENSES

Fourteenth Annual Clinical Session Expenses			
Salaries	\$ 2,999 19		
Communications (Postage, Etc )	394 14		
Stationery and Office Supplies	106 50		
Printing	1,179 63		
Traveling Expenses	3,149 89		
Auditorium Charges	746 56		
Honorarium	50 00		
Entertainment	409 50		
Advertising	857 05		
Reporting	422 49		
Badges	314 48		
Ladies Committee	174 06		
Banquet ..	394 89		
Miscellaneous	<u>121 85</u>	\$11,320 23	
Forward		\$11,320 23	\$44,632 69

## EXPENSES (Continued)

Forward		\$11,320 23	\$44,632 69
Deduct			
Exhibits	6,900 90		
Guest Fees	1,046 00	7,946 90	
Net Expenses			3,373 33
Annals of Internal Medicine			
Expenses			
Salaries	4,805 56		
Communications (Postage, Etc )	1,045 85		
Stationery and Office Supplies	9 74		
Printing	13,742 50		
Traveling Expenses	25 08		
Miscellaneous	125 92	19,754 65	
Deduct			
Subscriptions			
Volume I	\$ 32 55		
Volume II	55 12		
Volume III	635 94		
Volume IV	14,887 90	15,611 51	
Advertising			
Volume III	2,182 12		
Volume IV	1,361 37	3,543 49	19,155 00
Net Expenses			599 65
Executive Secretary's Office			
Expenses			
Salaries	\$ 9,661 52		
Communications (Postage, Telephone, Etc )	1,030 03		
Stationery and Office Supplies	682 26		
Printing	912 20		
Rent and Maintenance	3,127 71		
Traveling Expenses	2,728 69		
Annual Audit	150 00		
Premium on Surety Bond	20 00		
Miscellaneous	192 45	18,504 86	
Treasurer's Office			
Expenses			
Salaries	470 00		
Communications (Postage, Etc )	20 00		
Stationery and Office Supplies	30 00		
Traveling Expenses	109 95		
Annual Audit	50 00		
Premium on Surety Bond	100 00		
Miscellaneous	30 00	809 95	
Annals of Internal Medicine Distributed Free to Life Members		84 00	
1930 Supplement (Cost of Production and Distribution)		823 33	
Depreciation on Furniture and Equipment		322 78	
Net Income for the Year			24,517 90
			\$20,114 79

ANNALS OF INTERNAL MEDICINE

COST ANALYSIS  
(Revised to March 10, 1931)

				Number of Pages	
		Scientific Matter	News Notes Covers, etc	Paid Advertising	Total
Volume II	July, 1928 to June, 1929	1195	254½	98½	1548
Volume III	July, 1929 to June, 1930	1133	248	163	1544
Excess pages, Volume II over Volume III		<u>62</u>	<u>6½</u>	<u>64½*</u>	<u>4</u>
Circulation, Volume I		1803	*Excess, Vol III		
Circulation, Volume II		1999			
Circulation, Volume III		2446			

Volume II				Volume III			
INCOME							
Subscriptions, segregated from dues at \$6 per mem- ber				\$10,080 00		\$11,184 60	
Direct subscriptions				2,210 02		3,725 80	
Gross Receipts				\$12,290 02		\$14,910 40	
Less Expenses				43 17	\$12,246 85	135 28	\$14,775 12
(Refunds, etc )							
Advertising							
Gross Receipts				\$ 2,019 93		\$ 3,311 34	
Less Expenses				239 59	\$ 1,780 34	186 51	\$ 3,124 83
					\$14,027 19		\$17,899 95
EXPENDITURES							
Salaries				\$ 3,709 88			\$ 4,274 89
Equipment, Net				11 10			
Postage and Telephone				684 09			945 95
Office Supplies				104 61			61 46
Printing				\$11,365 28		\$12,795 62	
Less Repayment for Excess Illustrations				\$261 42		\$121 69	
Less Inventory of Stock				451 25	712 67	813 29	934 98
Traveling Expenses					42 50		
Miscellaneous (Editor's Office Copyright, etc )					127 78		130 74
Cost					\$15,332 57		\$17,338 76
Volume II —Deficit						\$1,305 38	
Volume III—Surplus						561 19	

## APPRECIATION OF THE OATH

The New England Journal of Medicine (April 23, 1931, p 887) quotes editorially from the Oath Required of Candidates for Membership in the American College of Physicians and comments, in part, as follows

"Here is a code of ethics which should be endorsed by every practitioner \* \* \* Its spirit and application, if generally observed, should have a definite influence in the solution of many of the problems before the public. If the public can be led to believe that this high standard is the underlying principle of service, there will be less criticism of doctors and irregular practice will be more generally discredited. The solution of the problems of the cults is in the hands of doctors"

Dr Leon T LeWald, (Fellow), Professor of Roentgenology, New York University, addressed the County Medical Society at Schenectady, New York, on Tuesday evening, May 5th, 1931. The subject was "Paget's Disease (Osteitis Deformans) Summary of 73 Cases. Remarks on Endocrine Etiology. Relationship to Deafness. Unusual Manifestations (Tumor Formation) Lantern Slides"

Dr Fred Meixner (Fellow) delivered the Pi Sigma Phi Lecture before the faculty of Bradley College, Peoria, Illinois, on March 16th. The subject was "Modern Aspects of Health Education"

Dr H Hilton Shreve Read (Associated), Atlantic City, N J, presented two Clinics in April at the Jefferson Medical College, of Philadelphia, illustrating the practical procedures indicated in the care of diabetic patients in general practice. Dr Read had charge of the Diabetic Clinic in connection with the Medical Dispensary of the Jefferson Hospital for six years

Dr Archibald L. Hoyne (Fellow), Chicago, has been appointed Associate Clinical Professor in the Department of Pediatrics of the University of Chicago

Dr Henry A Christian (Fellow), Boston, Mass, addressed the William Harvey Society, April 10, on "The Old and New in General Practice"

Dr N Emmons Paine (Fellow), Newton, Mass, has been reappointed Chairman of the Board of Trustees of the Westboro State Hospital, and also re-elected Vice President and Member of Investment Bureau of the West Newton Savings Bank

Dr Louis Faugeres Bishop, Jr (Fellow), New York, N Y, has been elected a trustee of Rutgers University

Dr Dean B Cole (Fellow), Richmond, Va, was re-elected President of the Virginia Tuberculosis Association at its recent meeting

Dr Sinclair Luton (Fellow), St Louis, conducted a heart clinic at the recent meeting of the Union County Medical Society

Dr Luvia M Willard (Fellow), Jamaica, N Y, was recently elected to honorary membership in Alpha Omega Alpha, Cornell Chapter. Dr Willard is also Pediatrician of the Postgraduate Medical School and Hospital of New York City

Dr Joseph B Wolfe (Associate), Philadelphia, has been appointed Associate Professor of Cardiology at Temple University School of Medicine

Dr Linn J Boyd (Fellow), New York, N Y, is the author of the following articles which appeared in the March issue of the Journal of the American Institute of Homeopathy "Diabetes Mellitus" and "The Diagnosis of Pernicious Anemia"

The following members of the College participated on the program of the Philadelphia Heart Association, May 18 to 21, inclusive, as indicated

Dr Ross V Patterson (Fellow), Philadelphia—"A Rational Plan for the Diagnosis and Treatment of Heart Affections"

Dr Edward J G Beardsley (Fellow), Philadelphia—"Problems Associated with Aortic Regurgitation"

Dr Elmer H Funk (Fellow), Philadelphia—"Acute Endocarditis"

Dr Henry K Mohler (Fellow), Philadelphia—"Heart Block"

Dr Edward Weiss (Fellow), Philadelphia—"Congenital Heart Disease"

Dr William Egbert Robertson (Fellow), Philadelphia—"The Diagnosis of the Failing Heart Muscle"

Dr H Brooker Mills (Fellow), Philadelphia—"Heart Disease in Children"

Dr Joseph B Wolffe (Associate), Philadelphia—"Coarctation of the Aorta"

Dr E B Krumbhaar (Fellow), Philadelphia—"Demonstration of the Pathology of the Cardiovascular System"

Dr John Eiman (Fellow), Philadelphia—"Anatomy of the Conducting System with Demonstration of Injection of the Purkinje System and Demonstration of Injection of Coronary System"

Dr James E Talley (Fellow), Philadelphia—"Cardiovascular Phenomena of Thyroid Disease"

Dr S Calvin Smith (Fellow), Philadelphia—"Demonstration and Discussion of Electrocardiography in Diagnosis and Treatment of Heart Disease"

Dr Charles C Wolferth (Fellow), Philadelphia—"The Relation of Cardiology to General Medicine"

Dr David Riesman (Fellow), Philadelphia—"Some of the Difficulties in the Diagnosis of Mitral Stenosis"

Dr Truman Schnabel (Fellow), Philadelphia—"Diet and the Gastro-intestinal Tract in Relationship to Cardiovascular Disease"

The following Fellows of the College addressed the one-day clinical and scientific program bearing upon tuberculosis sponsored by the Nebraska Tuberculosis Association at the State Hospital at Kearney, April 30

Dr J A Myers, of Minneapolis—"Childhood Tuberculosis"

Dr Miles Breuer, of Lincoln, Nebr—"Diagnosis"

Dr Warren F Pearce (Fellow), Quincy, Ill, presented cases of hyperthyroidism at an all-day clinical meeting held by the Adams County (Ill) Medical Society on April 13, at Quincy,

Dr Harold Swanberg (Fellow), Quincy, Ill, addressed the same meeting on "Pre-radium Treatment of Carcinoma of the Cervix"

The New England Health Institute, held at Portland, Maine, April 20-23, was addressed by the following Fellows of the College

Dr Robert B Kerr, Manchester, N H "Health Education of the School Child"

Dr George W McCoy, Washington, D C "Contributions to Preventive Medicine from the National Institute of Health"

The eighty-five annual meeting of the Ohio State Medical Association was held at Toledo, May 12-13, under the Presidency of Dr Chester W Waggoner (Fellow), of Toledo Guest speakers included Dr Harry M Hall (Fellow), of Wheeling, W Va, who spoke on "The Doctor and Immortality"

Dr Frederick A Willius (Fellow), Rochester, Minn, addressed the tenth annual meeting of the Philadelphia Heart Association, April 15, on "Problems Underlying the Prevention of Heart Disease"

The annual meeting of the South Carolina Medical Association was held at Greenville, S C, May 5-7, under the Presidency of Dr Kenneth M Lynch (Fellow), of Charleston

Dr William H Mayer (Fellow), Pittsburgh, Pa, was one of the guest speakers at the annual meeting of the West Virginia Medical Association held at Clarksburg, May 19-21 Dr Mayer's subject was "The Nervous Patient and the Practitioner"

Dr Walter C Alvarez (Fellow), Rochester, Minn, addressed the Central Tri-State Medical Society, April 30, on "Practical

### Points in the Treatment of Gastro-Intestinal Diseases"

Dr Felix J Underwood (Fellow), President of the Southern Medical Association, recently appointed Dr Walter Baumgarten (Fellow), St Louis, a member of the Council from Missouri of the Southern Medical Association. Dr Baumgarten succeeds Dr W McKim Marriott (Fellow), St Louis, whose term has expired, and having served the constitutional limit, was not eligible for reappointment.

Dr J Stuart Pritchard (Fellow), Battle Creek, gave the first lecture, April 1, of a series of lectures on communicable diseases in progress at the Herman Kiefer Hospital, Detroit, under the auspices of the Wayne County Medical Society, in conjunction with the Urological, Dermatological and Tuberculosis Societies of Detroit. Dr Pritchard's subject was "Clinical Symptoms of Tuberculosis."

Dr Felix J Underwood (Fellow), Jackson, Miss., spoke before the fifty-second annual meeting of the Louisiana State Medical Society, April 14-16, on "Appraisal of County Health Work Based on Reduction of Morbidity and Mortality."

Dr Cyrus C Sturgis (Fellow), Ann Arbor, Mich., conducted a Clinic on pernicious anemia at the fifty-eighth annual meeting of the Northern Tri-State Medical Association, which was held at Ann Arbor, April 14.

Dr Anton J Carlson (Fellow), Chicago, addressed a joint meeting of the New York Academy of Medicine and the New York Gastro-Enterological Society, recently, on "Motor Mechanism of the Large Bowel."

Dr Walter M Simpson (Fellow), Dayton, Ohio, delivered an address on undulant fever at the Summitt County (Ohio) Medical Society on April 7.

On March 31, Dr George R Minot (Fellow), Boston, addressed the Vanderbilt University School of Medicine and the Nash-

ville Academy of Medicine on treatment of anemia.

Dr George E Pfahler (Fellow), Philadelphia, spoke before the Philadelphia Roentgen Ray Society, April 2, on "Demonstration of the Lymphatic Drainage of the Maxillary Sinuses."

Dr William Egbert Robertson (Fellow), Philadelphia, was the speaker at a Postgraduate Seminar of the Philadelphia County Medical Society, April 8, his subject being "Some Physiological Applications in Medicine."

Dr James B McElroy (Fellow), Memphis, delivered the Presidential address at the meeting of the Tennessee State Medical Association held at Knoxville, April 14-16.

Dr William A White (Fellow), Washington, D C., addressed the American Red Cross, April 13-16, on "Therapeutic Value of Hospital Social Service."

Dr Walter W Palmer (Fellow), New York, N Y, recently lectured at the School of Tropical Medicine of the University of Porto Rico.

Dr Walter C Alvarez (Fellow), Rochester, Minn., was one of the guest speakers at the eighty-fourth semi-annual meeting of the Southern California Medical Association held at Coronado Beach, April 17-11. Dr Alvarez's subject was "Diagnosis of Gastro-Intestinal Diseases from the History."

### New Life Member

Dr Roscoe L Sensenich (Fellow), South Bend, Ind., recently subscribed to the Endowment Fund of the College, thereby becoming a Life Member.

The following Fellows of the College participated on the program of the Oklahoma State Medical Association's meeting, May 11-13, at Oklahoma City.

Dr John H Musser, New Orleans—address

Dr A W White, Oklahoma City—"Gastro-duodenal Ulcer, Medical Aspects"

Dr Ray M Balyeat, Oklahoma City—  
"Recent Advancement in Allergy"

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Dr Carroll M Pounders (Fellow), Oklahoma City, delivered the Chairman's Address at the meeting of the Oklahoma Pediatric Society on May 11

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Colonel Charles F Craig (Fellow), Asst Commandant, Army Medical Center Washington, D C, has been elected a Corresponding Member of the Societe de Medicine & d'Hygiene Tropicales Egypte, and Secretary General of the Commission Scientifique d'etudes of the Federation Internationale des Societes de Medicine & d'Hygiene Tropicales, Paris

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Dr E J G Beardsley (Fellow), Philadelphia, addressed the Gloucester County (N J) Medical Society, April 16, on "The Importance of Routine Procedures to Insure Correct Diagnoses"

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Dr Bernard Langdon Wyatt (Fellow), Tucson, Ariz, has been elected by the Executive Council to active membership in the American Medical Editors' and Authors' Association

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Dr Konrad E Birkhaug (Fellow), Associate Professor of Bacteriology at the University of Rochester School of Medicine and Dentistry, has been elected a member of the Norwegian Academy of Sciences

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Dr Ralph O Clock (Fellow), New York, N Y, was the principal speaker at the annual meeting of the senior classes of the Schools of Science and Technology of Pratt Institute, Brooklyn, on March 25 Dr Clock's subject was "The Nation's Health," in which he emphasized the part played by chemistry in the development of medical science

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Dr John Dudley Dunham (Fellow), delivered an extra-mural lecture to the Senior Class at Ohio State University, April 23, 1931. His topic was "Diseases of the Esophagus," illustrated by lantern slides

Dr Earle E Mack (Associate), Syracuse, New York, was recently elected Secretary of the Onondaga Medical Society, and also Trustee of the Syracuse Academy of Medicine

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Dr Oliver T Osborne (Fellow), New Haven, Conn, is the author of an article entitled "Rising Tide of Narcotic Addiction Menaces Mankind" in the February 22, 1931, issue of the New Haven Register

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Dr Samuel M Feinberg (Fellow), Chicago, Ill, addressed the Saginaw (Mich) County Medical Society, February 17, on "Allergy"

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Dr Carl V Vischer (Fellow) of Philadelphia was recently elected Chief of the Medical Out-patient Department of Hahnemann Hospital, Philadelphia Dr Vischer is the author of an article, "Modern Advances in General Therapeutics," which appeared in the February issue of the Hahnemann Monthly

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Dr Howard T Phillips (Fellow), Wheeling, West Virginia, is the author of a paper entitled "Use and Misuse of X-Rays in Skin Diseases" in the February issue of the West Virginia Medical Journal

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Dr Will Gardiner (Fellow), Toledo, Ohio, was elected vice president of the staff at the annual meeting of the Women's and Children's Hospital of Toledo

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Dr Ellen C Potter (Fellow), Trenton, N J, Director of Medicine of the Department of Institutions and Agencies, was appointed Chairman of the Program Committee of the New Jersey Conference of Child Health and Protection, called by the Governor as part of the follow-up program of the White House Conference

The State Conference was held April 16-18 on the campus of the Woman's College at New Brunswick

The first State Conference on Mental Hygiene for the State of New Jersey was held in Newark, February 27, under the auspices of the Mental Hygiene Committee of the State Board of Control Dr Potter presided

in the absence of Commissioner Ellis. The purpose of the conference, which brought together ninety-five psychiatrists, psychologists and psychiatric social workers, was to determine state policy in this field.

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Dr N Worth Brown (Fellow), Toledo, Ohio, has been appointed Lieutenant Colonel of Medical Reserves, U S Army, attached to the 83rd Division and assigned to the Toledo Mobilization Center.

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Dr Thomas W Durbin (Associate), Director of Medicine at the Flower Hospital of Toledo, Ohio, and Dr N Worth Brown (Fellow), Chief of the Medical Service of the Toledo Hospital, have joined the newly established "Toledo Clinic," a group which includes representatives from each special field in medicine and surgery, and which is associated through its members with the staff work of five Toledo hospitals.

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Dr George R Minot (Fellow), Director of the Thorndike Memorial Laboratory, Boston City Hospital, addressed the Alpha Omega Alpha Chapter of Vanderbilt University Medical School at Nashville, Tenn, March 31, on "The Treatment of Anemia." Dr Minot addressed the Harvard Medical Alumni Association, April 17, on the same subject.

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Dr Albert F R Andresen (Fellow), N Y, read a paper on "Newer Aspects of Peptic Ulcer" before the Flatbush Medical Society on January 9, and on "Medical Treatment of Gastro-duodenal Ulcer," before the Queens County Medical Society on January 27.

Dr Andresen also gave a popular lecture at the Prospect Branch, Young Men's Christian Association, under the auspices of the Public Health Committee of the Medical Society of the County of Kings, January 16, his subject being, "Constipation."

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Dr Curran Pope (Associate), Louisville, Ky, delivered a radio address over the radiophone of WLAP, Louisville, Ky, February 22, "George Washington, Soldier and Statesman."

Dr Oliver T Osborne (Fellow), New Haven, Conn, is the author of an article entitled "The Relation of Medicine to Dentistry" in the American Journal of Stomatology, January, 1931, page 43, Vol IV, No 2.

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Dr John Kerr Pepper (Fellow), Winston-Salem, N C, was recently elected President of the North Carolina Radiological Society. Dr William T Ramey (Fellow) of Fayetteville, N C, was elected vice president.

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Dr Charles J Bloom (Fellow), New Orleans, addressed the Tangipahoa Parish Medical Society, April 2, on Infant Feeding.

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The Faculty of Medicine of Paris (The Medical School of the University) announces that, during June and July, 1931, a comprehensive series of postgraduate courses will be presented. The enterprise is conducted under the auspices of the Association for the Development of Medical Relations (the "A D R M") a commission sponsored by the French Government.

The work will be presented in the English language. Clinics, lectures and demonstrations will be conducted in the great hospitals of Paris, on a wide variety of topics, by the most eminent French clinicians. A nominal fee will be charged for each course. Upon the completion of each course, the student who qualifies will receive a certificate covering the work, signed by the professor in charge.

Detailed information may be secured by addressing direct, Professeur E Hartmann, President, "A D R M," Faculty of Medicine of Paris, 12, Rue de L'Ecole de Medicine, Paris (6e) or, in the United States, Doctor Frank Smithies, 920 N Michigan Avenue, Chicago, Ill.

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#### GIFTS TO THE COLLEGE LIBRARY

Acknowledgement is herewith made of the receipt of the following publications by members of the College.

Dr Walter M Simpson (Fellow), Dayton, Ohio, 1 book, "Tularemia."



Dr Chas Hartwell Cocke, (Fellow),  
Asheville, N C 11 reprints,

"Time and Tuberculosis"

"Pneumothorax Therapy in Tuberculosis"

"Pneumothorax Therapy—A Consideration of its Value and Apparent Neglect"

"Early Pulmonary Tuberculosis"

"Chronic Familial Hemolytic Jaundice or Banti's Disease"

"Albumin in the Sputum in Tuberculosis its Value in Diagnosis and Prognosis"

"Massive Atelectasis"

"Spontaneous Pneumothorax Following Artificial Pneumothorax, with Operation and Recovery"

"Tuberculin"

"Early Diagnosis of Pulmonary Tuberculosis—the Essential Factor in Prevention and Cure"

"Vaccines in the Treatment of the Secondary Infection in Pulmonary Tuberculosis"

Dr William D Reid (Fellow), Boston, Mass 1 reprint,

"The Differential Diagnosis of Subacute Bacterial Heart Disease and Banti's Disease Case Report"

Dr Karl Rothschild (Associate), New Brunswick, N J 2 reprints,

"Familiäres Auftreten von Polycythaemia Rubra in Verbindung mit Chorea Progressiva Hereditaria Huntington" (with H. Doll)

"Die Chorea Huntington—Familie R"

Dr Elwood A Sharp (Fellow), Detroit Mich 1 reprint,

"The Relation of Toxicity to Dosage of Tetrachlorethylene"

Dr. C F Tenney (Fellow), New York City 6 reprints,

"A General Survey of the Visceral Neuroses" (with W H Squires)

"Systemic Manifestations of Vincent's Infection"

"Monilia Pneumonia"

"Pericious Anemia" (with Jos Lintz S D Jessup & Harlow Brooks)

"Certain Clinical Observations on Gastric Ulcer"

"Effects of Intravenous Injections of Acriflavine in Sepsis" (with Jos Lintz)

Dr Philip King Brown of San Francisco, a guest speaker at the 1930 (Minneapolis) Clinical Session of the College, has also contributed the following reprints

"Peptic Ulcers—Diagnosis and Treatment"

"Thoracoplasty in the Treatment of Pulmonary Tuberculosis"

"The Cost of Private Practice"

Dr Miles J Breuer (Fellow), Lincoln, Nebr 2 reprints,

"The Fatigue Conscience in Tuberculosis"

"Pulmonary Tuberculosis without Lung Symptoms"

Dr Edward E Cornwall (Fellow), New York, N Y 3 reprints,

"Suggestions for the Dietetic Treatment of Heart Failure"

"Arterial Peristalsis and Essential Hypertension"

"A Primer of Pneumonia Therapeutics"

Dr Charles F Craig (Fellow), Washington, D C 12 reprints

"The Diagnostic Value of the Complement Fixation Test in Amebic Infections"

"The Prophylaxis and Treatment of Amebiasis"

"The Technique and Results of a Complement Fixation Test for the Diagnosis of Infections with *Endamoeba Histolytica*"

"The Nuclear Structure of *Dientamoeba Fragilis*"

"A Comparison of the Practical Value of the Wassermann and Kahn Tests in the Diagnosis of Syphilis in the Military Service"

"Directions for Making the United States Army Typhoid-Paratyphoid 'A' Vaccine"

"Observations Upon the Hemolytic, Cytolytic and Complement-Binding Properties of Extracts of *Endamoeba Histolytica*"

"The Value of Cultural Methods in Surveys for Parasitic Amebae of Man"

- "A Simplified Method for the Cultivation of *Endamoeba Histolytica*"
- "The Relation of Officers of the Medical Corps to Scientific Medicine"
- "Observations Upon Complement Fixation in Infections with *Endamoeba Histolytica*"
- "Complement Fixation in the Diagnosis of Infections with *Endamoeba Histolytica*"
- Dr Joseph R Darnall (Fellow), Washington, D C 5 reprints,  
 "A Case of Chloroma of the Sacrum"  
 "Modern Conception and Rational Treatment of Diabetes Mellitus"  
 "Dietetic Management of Cardiac, Vascular, and Renal Disease"  
 "The Application of Occupational Therapy to Chronic Medical Cases"  
 "Diet in Heart and Kidney Disease"
- Dr C Ray Lounsberry (Fellow), San Diego, Calif 1 reprint,  
 "Dermatological Neurosis"
- Dr William D Reid (Fellow), Boston, Mass 1 reprint,  
 "Heart Murmurs in the Practice of Medicine"
- Dr Lea A Riley (Fellow), Oklahoma City, Okla 1 reprint,  
 "A Surgical Diabetic"
- Dr James S Simmons (Fellow), Washington, D C 22 reprints,  
 "The Isolation and Cultivation of Tubercle Bacilli Protected from Light"  
 "Dengue Fever"  
 "Malaria on the Island of Corregidor, P I"  
 "A Malaria Survey at Fort Stotsenburg, P I"  
 "The U S Army Medical Department Research Board"  
 "An Acidfast Organism Isolated from a Mouse"  
 "Bactericidal Action of Mercuriochrome—220 Soluble and Iodine Solutions in Skin Disinfection"
- "The Intravenous Use of Acriviolet and of Mercurochrome in Bacterial Infections"
- "A Culture Medium for Differentiating Organisms of Typhoid-Colon Aerogenes Groups and for Isolation of Certain Fungi"
- "The Chronic Typhoid Carrier State Following Typhoid Infections in Vaccinated Individuals"
- "Negative Blood Cultures in Subacute Bacterial Endocarditis—Report of Two Cases"
- "A Comparison of the Schulte-Tigges and Ziehl-Neelsen Methods for Staining Acid-Fast Bacteria"
- "The Presence of Virulent Tubercle Bacilli in Human Bile"
- "Virulent Diphtheria Bacilli Carried by Cats"
- "Experimental Studies of the Treatment of Surra"
- "Observations on Equine Dhobie Itch of the Philippines"
- "The Use of Tetanus Antitoxin in the Protection of Horses Against Infection by *Clostridium Tetani*"
- "The Prevalence and Distribution of Malaria on the Island of Corregidor, P I"
- "Bacteriological Data on the Chlorine Treatment of Respiratory Diseases"
- "Diphtheria Infections, with Particular Reference to Carriers and to Wound Infections with *B Diphtheriae*"
- "Diphtheria Bacilli from Postoperative Empyema Wounds"
- "Dermatitis Venenata Produced by an Irritant Present in the Stem Sap of the Mango (*Mangifera Indica* L.)"
- Dr Carl V Vischer (Fellow), Philadelphia, Pa 1 reprint,  
 "Modern Advances in General Therapeutics"

## OBITUARY

## CHARLES BRADFORD McABOY

Charles Bradford McAboy, Ph B, M D (Associate), who was born in Butler, Pa, July 29, 1875, and was graduated from the University of Pennsylvania School of Medicine in 1901, died at his home in the East End, Pittsburgh, Pa, February 5, 1931, of cerebral hemorrhage. Dr McAboy was physician to the Columbia Hospital, Wilkensburg, was a valued member of his state and county med-

# The Electrocardiogram in Angina Pectoris

By MORRIS H. KAHN, M.A., M.D., *New York City*

**A**N abundance of literature is devoted to the syndrome of angina pectoris. And yet after two decades of the intensive use of the electrocardiograph in diagnosis in these cases, no general opinion has been reached as to the pathologic changes that underlie this distressing disease. The reason for this is to be found in the fact that angina pectoris is not a pathological entity. It is rather the clinical manifestation of disease processes in the heart muscle, in the coronary arteries or in the aorta, producing pain of more or less typical character. We must accept the possibility of different lesions in different cases. On this account we cannot *a priori* expect unfailing assistance from the electrocardiogram either in the diagnosis of these cases or in the prognosis.

In his book on this subject Sir James Mackenzie knowingly omits all discussion of the electrocardiograms of his cases, each of which he so carefully reviews from a clinical diagnostic standpoint. Sir Clifford Allbutt comes to the conclusion that the electrocardiogram cannot reveal intrinsic functional values in the heart's capacity, but he does not discuss its diagnostic value in angina pectoris. Harlow Brooks in an excellent monograph on the subject emphasizes that the *value* of electrocardiographic findings does not

exclude angina. He states, on the contrary, that "any electrocardiographic finding which indicates, in so far as the electrocardiogram may disclose of the heart muscle or of the coronary vessels is to be considered as highly confirmatory evidence when the clinical aspects of the case suggest angina. Serious consideration should be given to positive cardiographic findings even in the absence of clinical evidence if these findings are of sufficiently definite and constant character. Negative findings are to be considered clinically as merely negative findings and much clinical weight must not be attached to them."

We have been led to the same conclusion as a result of the analysis of the electrocardiograms of our series of three hundred and thirty cases of clinical angina pectoris which have been under our observation for a number of years. In this paper we shall present the data correlating them with other and interesting clinical facts.

other records. Thus the P wave, the P-R interval, the QRS wave, the S-T phase, the T wave and the intercycle period may each or all present notable variations from the normal. It would be almost impossible to classify electrocardiograms if every detailed alteration from the normal were given equal weight. Secondly, electrocardiograms naturally alter with the advent of time and the concomitant effects of senescence and with the development of pathological processes in the heart. Progressive changes are all the more likely in individuals in whom disease has already produced severe clinical symptoms. Therefore, repeated films, taken at intervals of months or years, often show remarkable differences one from the other. Such cases would

most notable electrocardiographic features in each case. The electrocardiogram was negative in 54 cases, or 16% of the series, in which cases it showed no significant abnormality. Left ventricular preponderance, which must be considered a negative feature in diagnosis, was noted in 83 otherwise negative records or 25%. Right ventricular preponderance, on the other hand, occurred in only two cases. The T wave was inverted in Lead I in 39 cases, or 12%, and it was inverted in Lead 3 in 102 cases, or 31%. A typical so-called Coronary T wave was observed in only 12 cases, or 3.6%. The QRS wave was widened in 20 cases, or 6%, and the S-T phase was strikingly abnormal as an only feature in one case. Low voltage was the sole feature in 10 cases, or 3%. Bundle branch lesions were present in 7 cases,

TABLE OF ELECTROCARDIOGRAPHIC FINDINGS IN ANGINA PECTORIS

EKG Findings	No of Cases	% of Cases	No Died	% Died
Negative	54	16	5	9
plus Left Ventr Prepon	77	23	1	1.3
plus extrasystoles	5	1.5	2	.40
plus Auric Fibrillation	1	0.3	0	
Total Negative	137	41	8	6
Right Ventricular Preponder	1	0.3	0	
plus Auric Flutter	1	0.3	0	
Total Right Ventr Prep	2	0.6	0	
T-1 Inverted	10	3	3	30
plus L V P	29	9	1	3
Total T-1 Inverted	39	12	4	10
T-3 Inverted	31	10	2	6
plus L V P	71	21.5	1	1
Total T-3 Inverted	102	31	3	3
Coronary T Wave Observed	12	3.6	3	25
Q R S Widened	20	6	5	25
S-T Phase Abnormal	1	0.4	0	
Low Voltage	10	3	1	10
Bundle Branch Lesions	7	2	4	57
Total Number Of Cases	330		23	7

size and with the pathologic changes were fatal and of those with inverted

sive myocardial disease is present. It must be remembered that in angina pectoris this is usually absent.

#### FATAL CASES WITH EKG NEGATIVE

**Case 1** Mrs I L B, aged 50, had for two years sudden attacks of dizziness and for some weeks dyspnea and palpitation and fatigue on exertion. Precordial pain was felt under the left breast. The heart showed an atheromatous systolic blow over the apex and the aortic area, and the blood pressure was 198 over 110 mm of mercury. Three years later the precordial pain was more severe and there were attacks of severe pressing sensation across the sternum, the pain radiating to the left shoulder, with pallor, weakness and dyspnea. The heart rate was 120 despite the adequate doses of digitalis that were given, extrasystoles were frequent, the heart percussed enlarged to the right and left, and the apex beat was forceful out of proportion to the faintly audible first sound. Clinically the diagnosis of angina pectoris was made and aneurysm of the left ventricle was suspected to exist. *The electrocardiogram was negative.* The attacks of precordial distress and marked oppression in the chest became more severe, and in a short time sudden death occurred.

**Case 2** Mr Meyer B, aged 51 years, had felt dyspnea on exertion for six years. For eight months he felt a pressing sensation after exertion across the upper sternum and upper precordial region, the pain at times radiating into the left shoulder, both upper arms and the back of the chest. These

attacks were at times quite severe, and the patient was always compelled by the feeling of constriction across the chest to stop after walking two city blocks. The attacks were relieved by the inhalation of amyl nitrite. The heart showed a faint systolic aortic murmur, and frequently a tender spot high up in the left axilla, the blood pressure varied during the three years of observation between 146 over 88 and 176 over 100. *The patient was seen often, electrocardiograms were taken repeatedly, and they were always essentially negative.* The day after he was last seen, after walking up some stairs the patient had a severe attack of angina pectoris with coronary closure and cyanosis and died. *The electrocardiogram from this case is reproduced in Figure 1.*

**Case 3** Alexander H, a painter, aged 47 years, gave a history of untreated syphilis at the age of 22. For two years he had dull sternal pain and a feeling of oppression on exertion and after excitement which sometimes radiated to the left precordial region and into the left elbow-joint. Such attacks latterly occurred after walking half a block with palpitation and dyspnea. The aortic second sound was sharply accentuated, and there was audible a blowing systolic aortic murmur. The blood pressure was 130 over 55. The patient was seen in an anginal attack, in which while dressing he had to remain standing quietly for five minutes with pain over the manubrium. *The electrocardiogram showed no abnormalities.* Subsequently during a severer attack of angina pectoris the patient died suddenly.



DAVID H A

LOUIS M

MICHAEL S

MEYER B

ISRAEL L

FIG 1 Electrocardiograms from the group of cases of angina pectoris which showed negative electrocardiograms

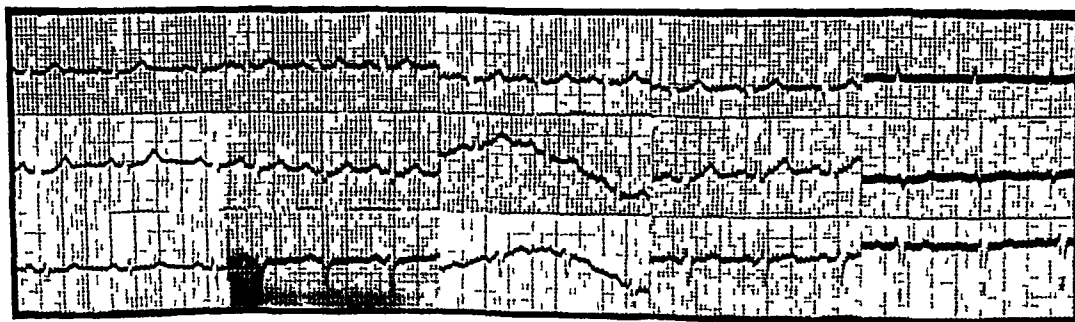
*Case 4* Israel L., aged 52 years, complained of pain across the front of the chest for several years with attacks of palpitation and a feeling of oppression behind the sternum, the pain lasting five to fifteen minutes radiating to the left upper arm and back, with a feeling of mortal anguish. *The electrocardiogram was negative* and yet the patient died suddenly shortly after in a typical attack of angina pectoris (Figure 1)

*Case 5* Mr Louis M., a farmer, 67 years old, developed attacks of precordial pain, with a distressing burning sensation across the sternum which developed even after mild exertion several times daily, together with a feeling of weakness, severe pallor and profuse perspiration. The heart beat was felt very faintly, the sounds were poor and inaudible at the base, but there was roughening of the systolic sound at the apex. There were tender spots in the precordial area. *The electrocardiogram was negative but for a rare extrasystole and sinus bradycardia* (See Figure 1). The blood pressure was 112 over 70 mm of mercury. Eight months after the patient came under our observation, repeatedly showing negative electrocardiograms, he died suddenly, in a severe attack of angina pectoris.

*Case 6* Mr Sol M., aged 47 years, had several attacks of "acute indigestion" four years before he came under our observation, in which the sudden pain radiated up to the throat. Six months before his first visit, he had such a sudden attack, with pain in the

upper dorsal region, radiating into both arms, and on attempting to move the pain became terribly severe in the lower sternal region, with extreme pallor and cold sweat, and dyspnea, and morphine was ineffectual to relieve it. Gradually the pain radiated to the left upper pectoral region, which became very tender to touch, and the patient had to stay for three weeks abed before he felt improved. Since then, after walking a block, pain returned in the mid-dorsal spine with weakness and dyspnea which were relieved by rest. Several attacks of vise-like pain in the precordium recurred with a sensation of clutching in the right side of the throat and pain in the right lower face. The heart apex was visibly forceful, but on auscultation the first sound was contrastingly weak, with audible systolic gallop rhythm. *The radial pulse showed distinct pulsus alternans, but the electrocardiogram showed only left ventricular preponderance.* The blood pressure was 150 and 146 over 94 mm of mercury, the liver was enlarged, and a diagnosis of angina pectoris was made with aneurysm of the left ventricle. Despite extreme care and absolute rest, the patient died shortly after in an attack.

*Case 7* Mr Melville J. S., a retired banker, aged 57 years, complained for two and a half years of a burning distressing feeling across his chest which came on while walking or climbing stairs, with some dyspnea and occasional feeling of faintness and palpitation. The blood pressure was 140 over 90, but the heart sounds seemed fair in



LOUIS P

JULIUS P

GUSSIE S

JOSEPH W

FIG. 2. Electrocardiograms from the group of cases of angina pectoris which showed only left ventricular preponderance.



quality *The electrocardiogram showed only left ventricular preponderance, on repeated examinations over a period of two years. The patient then died suddenly with an attack of angina pectoris.*

#### FATAL CASES WITH T INVERTED IN LEAD I

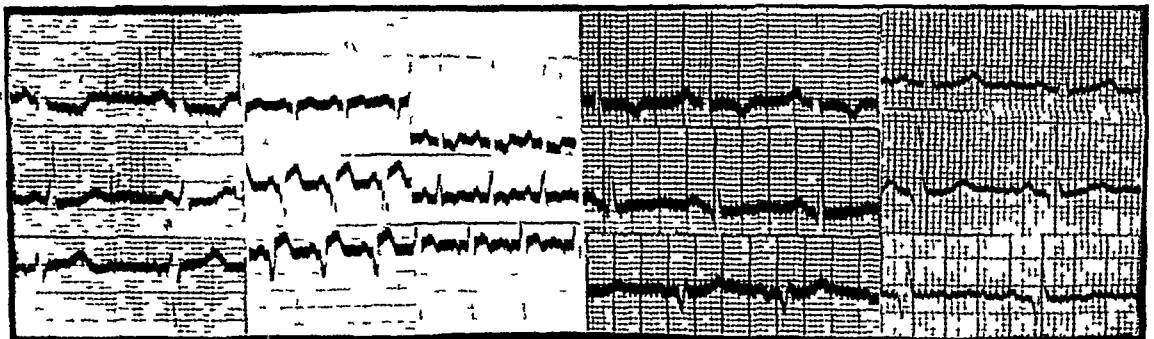
**Case 1** Mrs Fanny W, aged 60 years, developed pressing pain in the middle of the chest, and suddenly had a severe attack which compelled her to lie down with palpitation, pallor, dyspnea, and an agonizing feeling of anxiety as if she were dying. The pain radiated directly to the spine, and was relieved by morphine only after three hours. Milder attacks and an occasional severe attack occurred, and the patient gradually developed dyspnea and palpitation on exertion. The heart was enlarged toward the left and its sounds were of poor muscular quality. The blood pressure was 158 over 88. The condition lasted under our observation for a period of seven years after which the patient died. *The electrocardiogram showed only left ventricular preponderance and partial inversion of the T wave in Lead I, it was otherwise negative.* (See Figure 3)

**Case 2** Mr Max B, a tailor, aged 48 years, had a sudden pressing sensation in the midsternal region, with a numb drawing sensation across the chest and down the middle of both arms to the front of the wrists. He had profuse cold sweat and pallor with it, and the attack lasted twelve hours. Following that attack he had continuous precordial pain and frequent less severe attacks. The heart was slightly en-

larged, the sounds were of poor quality, and there was a systolic blowing murmur at the apex. The blood pressure was 120 over 112, and the peripheral vessels were somewhat tortuous. *The electrocardiogram showed inversion of the T wave in Lead I.* The patient died of myocardial failure after two years of observation.

**Case 3** Harry I, a chauffeur who had a positive blood Wassermann test, at the age of 49 years, was taken with sudden sharp severe pressing pain in the middle of the lower sternal region, with pallor and cold sweat. The attack lasted three hours. Such attacks recurred often at night, waking the patient, always with pallor and cold sweat. The pain radiated through to the back and down both arms to the elbows. After walking a block he had to stop because of pain and later also dyspnea and palpitation. The heart was very much enlarged with double aortic murmur and peripheral vessel tortuosity. The patient died with cardiac asthma and anginal pain. *The electrocardiogram showed inversion of the T wave in all three leads, more in Lead I than in Lead 3.* This case may be grouped with the cases showing Coronary T. (See Figure 5)

**Case 4** Perez B, aged 54 years, developed burning pain behind the sternum, which soon became constant and radiated to the precordial region and to the middle of the back. He was seen in an attack of dyspnea, cyanosis of the lips, complaining of pain in the epigastrium and in the precordial regions. *One electrocardiogram*



FANNY W

PEREZ B

MR I L P

JOSEPH H

FIG 3 Electrocardiograms from the group of cases of angina pectoris which showed T inversion in Lead I

*showed only left ventricular preponderance. A few days later it showed marked QRS notching in Leads 2 and 3, and the foot points of QRS were separated. The T wave was continuous from R. (See Figure 3).* Four days later the patient became restless, with anxious face, dyspnea, severe substernal distressing pain and profuse perspiration. Twenty minutes later the breathing became very difficult, râles filled the chest, extrasystoles developed with a heart rate of only 70, and death took place with pulmonary edema.

**Case 5** Mr I L P, a retired banker, aged 51 years, had several severe attacks of angina pectoris, which occurred regularly after walking one or two blocks even on level ground. *The electrocardiogram showed only inversion of T in Lead 1.* In a severe attack of coronary closure, after a few years of observation, the patient died. (See Figure 3)

#### FATAL CASES WITH T INVERTED IN LEAD 3

**Case 1** Joseph H, at the age of 57 years had a sudden attack of burning pain over the sternum radiating down the left arm to the fingers and compelling the patient to rest standing for five minutes. After that he had a burning sensation across the chest after exertion. A severe attack, with a feeling of imminent death, extreme pallor and cold sweat occurred a year later, with constricting pain in the upper abdomen radiating up to the front of the chest, and a severe burning sensation radiating down the left arm and hand. At that time he became

cyanosed and almost pulseless. Moderately severe and milder attacks recurred, often with cyanosis, pallor and cold sweat and a feeling as if he were dying. The heart was not enlarged, the sounds were of fair quality, and the blood pressure was 150 over 90 mm of mercury. After five years of such attacks *the electrocardiogram showed only slight inversion of T in Lead 3.* Several severe attacks occurred within a month while the patient was kept at absolute rest, and the patient died. (See Figure 3)

**Case 2** Dr George A M, began to have anginal pain across the chest with simultaneous pain in both forearms when he was 56 years old. After eight years of this disease, the heart sounds were poor in quality, the heart was not enlarged, and the blood pressure was 146 over 80 mm of mercury. *The electrocardiogram showed the T wave inverted in Lead 3,* but no other abnormality. Within a month after the last electrocardiogram, without premonitory symptoms, the patient died suddenly while seated in a train.

**Case 3** Michael S, a jeweler 43 years old developed after exertion a sudden jamming pain across the front of the chest, which was relieved after resting for one hour. It recurred as a feeling of a lump at the upper sternum and again as an attack of epigastric pressing during the night with dyspnea and a burning sternal sensation. The heart and aorta percussed enlarged with poor first sound, and a blood pressure of 144 over 88. *The electrocardiogram showed only slight*

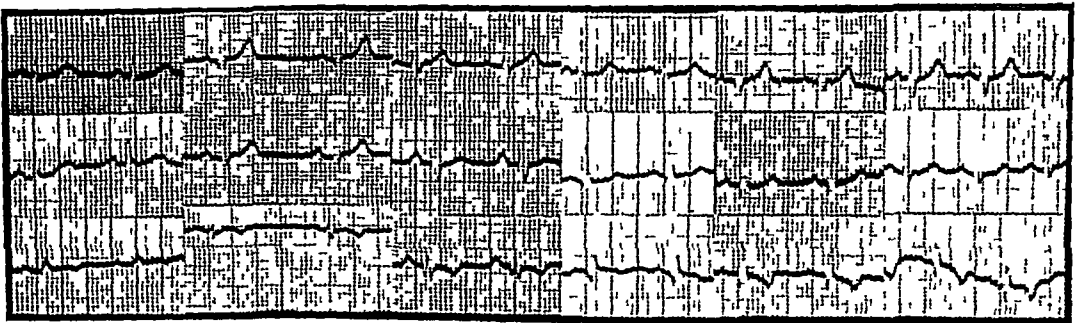


FIG 4 Electrocardiograms from the group of cases of angina pectoris which showed T inversion in Lead 3

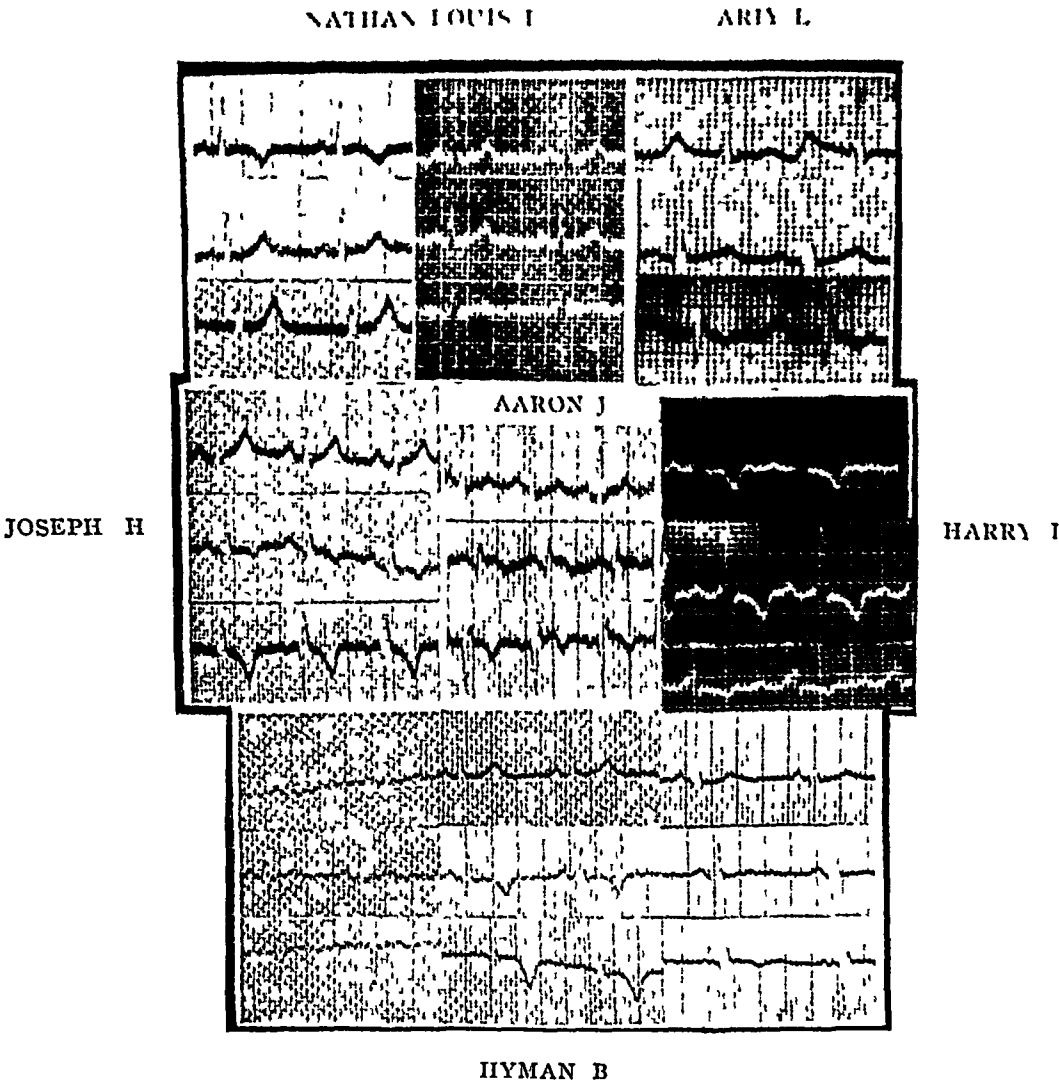


FIG 5 Electrocardiograms from the group of cases of angina pectoris which showed coronary T wave changes after a severe attack

*Case 2* Ary L., 61 years old, had for fifteen years frequent burning sensation over the lower sternum, and dyspnea on exertion. On July 6, 1926, a sudden sharp burning sensation shot across the precordium to the middle of the left arm. He also felt a constricting pain across the chest which was relieved after an hour by morphine and nitroglycerine. Similar milder attacks recurred after walking up grade. Except for a tender spot over the aortic region the heart examination was negative. The blood pressure was 136 over 88. *The electrocardiogram showed left ventricular preponderance and a Coronary T wave in Leads 2 and 3* (See Figure 5).

*Case 3* Mr Nathan Louis F., aged 54 years had a sudden attack of severe sticking pain in the middle of the chest, radiating to the left arm. Physical examination showed a sallow pallor, but otherwise the heart examination was negative. *The electrocardiogram showed left ventricular preponderance and complete inversion of the T wave in Lead 1*. This was interpreted as the coronary form of T wave, and the diagnosis of angina pectoris was made. For four years the patient continued in fair health, complaining of only occasional pressing sensation across the sternum which was relieved by nitroglycerine. *His electrocardiogram became normal*. He then began to have severe attacks of typical angina, which continue to occur frequently at the present writing (See Figure 5).

*Case 4* Mr Joseph H., 44 years old, while walking had a sudden cramp-like sensation in the front of the left shoulder shooting down the arm, with cold perspiration. He ran into a hallway and rested but that night the attack recurred and lasted all night. From that time on he had pain on walking which frequently radiated to the little finger of the left hand and once he fainted in such an attack. The examination showed the presence of diabetes and moderate arteriosclerosis, and *the electrocardiogram showed a marked Coronary T wave* (See Figure 5).

*Case 5* Aaron J. a tailor sixty-five years old had his first severe attack of anginal

pain on walking up two flights of stairs. The pain across the chest radiated toward the left shoulder, and was associated with dyspnea and palpitation. He had dyspnea and nocturnal asthma. The heart was enlarged to the left and there was a palpable thrill over the apex and aortic region with a rumbling systolic murmur. *The electrocardiogram showed left ventricular preponderance, the T wave inverted in Leads 2 and 3, with abnormality of the S-T phase* (See Figure 5). The heart showed occasional extrasystoles and periods of auricular flutter which subsided under the use of quinidine. The patient remained in bed with progressive myocardial failure and died suddenly.

#### COMMENTS AND CONCLUSIONS

We deemed it desirable for the sake of emphasis and for purposes of critical presentation to outline the main features of the cases that are here recorded and to reproduce the illustrative electrocardiograms, in order that the reader may perceive at a glance the relative unimportance of the electrocardiogram in the clinical diagnosis of angina pectoris.

We may therefore conclude this paper with the following general assertions:

- 1 The diagnosis of angina pectoris rests on the clinical features, particularly on the symptomatic attacks.

- 2 In cases of clinical angina pectoris any abnormality of the electrocardiogram, however trivial, may be significant.

- 3 The alteration in form of the T wave following a minor attack is a gradual one, except where there is massive occlusion, so that every alteration is important.

- 4 In order that the electrocardiogram should serve best in diagnosis

frequent records should be made at intervals

5. A series of three hundred and thirty cases of typical angina pectoris is analyzed, of which twenty-three or seven per cent died during an attack

6. Of all the cases, one hundred and thirty-seven, or forty-one per cent showed negative electrocardiograms during the entire period of observation.

7. Of the total cases thirty per cent had negative or insignificant electrocardiograms during the entire time of our supervision

8. In the evaluation of the electrocardiogram as an aid in the diagnosis of angina pectoris, it must be remembered that negative findings must be dismissed from consideration while even trivial findings may have weighty significance in diagnosis

# The Relationship of Pain to Jaundice\*

JAMES F WEIR, M D , *Division of Medicine, The Mayo Clinic,*  
*Rochester, Minnesota,*

*and*

WALLACE T PARTCH\*\*, M D , *Welborn Hospital Clinic, Evansville, Indiana*

IN THE last decade certain adjustments have been made in our conception of jaundice. This has been due largely to the application by van den Bergh of Ehrlich's diazo reagent to the blood serum and to the demonstration by Mann and his associates, and others, that bilirubin forms chiefly outside the liver and that the polygonal hepatic cell is the normal pathway of excretion of bilirubin. Jaundice may be produced in one of three ways: obstruction of the biliary passages, increased production of bilirubin beyond the ability of the liver to excrete it, or functional derangement of the polygonal hepatic cell interfering with the excretion of the pigment. On this basis, McNee proposed that jaundice be classified into three clinical types: obstructive, hemolytic, and toxic or infectious. We have found this a practical classification.

Numerous pathologic processes lead to the development of jaundice, and one is often impressed with the extreme difficulty frequently encountered in

making a satisfactory clinical diagnosis. Many factors in the clinical history, the physical condition, or laboratory data enter into this evaluation. McVicar and Fitts suggested that the essentials of a workable procedure include (1) the character of the van den Bergh reaction, (2) the height and behavior of the serum pigment curve, (3) the quantity of bile reaching the intestines as determined by siphonage of the duodenal contents, and (4) the presence or absence of pain and its character. The clinician's first duty in such cases is to separate them into surgical and nonsurgical groups; we believe that pain is one of the most significant single factors in such differentiation.

## TYPES OF PAIN

We are presenting a review of 275 consecutive cases of jaundice recorded in The Mayo Clinic between 1926 and 1928 inclusive with regard to the frequency of occurrence, general character, duration and site of pain, and the relationship of pain to the onset of icterus. It is important to ascertain the time relationship of the pain with respect to the onset of jaundice, if pain occurred within one month of the

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\*\*Work done while a Fellow in Medicine, The Mayo Foundation, Rochester, Minnesota.

recognition of the jaundice we arbitrarily assumed the possibility of relationship. Although there are exceptions to every generalization, as will be shown pain associated with jaundice is usually indicative of obstruction of the biliary tract. A summary of the data is given in tables 1 and 2. Various types of pain are encountered: (1) typical colic; (2) colic atypical as to character or site; (3) pain of a dyspeptic nature, gaseous or ulcer-like; (4) constant or boring pain; and (5) miscellaneous associated pain.

*Typical colic*—The so-called biliary colic is the most common type. In its typical form it is characterized by sudden, severe pain in the epigastrium or right upper part of the abdomen, often requiring opiates for relief and often radiating to the right subscapular re-

gion. Associated symptoms include diaphragmatic spasm interfering with free respiration, gastric disorders such as belching, nausea, and vomiting, and various degrees of shock manifested by weakness, perspiration, pallor, acceleration of pulse, and prostration. The pain may cease suddenly, often leaving tenderness.

There is no satisfactory explanation of the mechanism of the colicky pain in disease of the biliary tract. This was considered by Graham and his associates, who stated: "In the absence of any positive evidence one is forced to conclude that the origin of the pain cannot be satisfactorily explained at the present time."

Typical colic in definite association with jaundice was present in 136 cases of this series. One hundred seventy-

TABLE 1  
275 CONSECUTIVE CASES OF JAUNDICE

Major Pathologic Condition	Cases	Colic		Atypical Pain		Painless onset	Pain later
		Recent	Previous	Recent	Previous		
Stones in common duct (no previous operation)	59	45	49	9	17	9	2
Stones in common duct (previous operation)	45	35	40			10	
Total	104	80	89	9	17	19	2
Benign stricture of common duct	49	22	41	8		27	
Malignant lesions							
Ducts, ampulla, and duodenum	9	1		1	1	7	
Head of pancreas	38	5	8	13	6	19	2
Gallbladder with extension to ducts	5	1	2			3	2
Liver (metastatic)	7	1	3	2		3	2
Total	108	30	54	24	7	59	6
Chronic cholecystitis with stones	25	14	17	3	2	8	4
Miscellaneous: cholangitis, biliary cirrhosis, "intrahepatic," indeterminate	38	12	16	5	7	21	1
Total	63	26	33	8	9	29	5
Total	275	136	176	41	33	107	13

six patients gave a history of colic at some time during the course of their illness. Colic occurred most frequently in conditions associated with calculi, cholangitis, and strictures. However, it occurred in enlargements of the head of the pancreas quite frequently, occasionally, in cases of apparent primary hepatic disease there is sufficient pain to cause difficulty in arriving at an accurate clinical diagnosis.

*Atypical colic*—Atypical colic both as to character and situation may vary from acute attacks of more or less severe epigastric discomfort, distention, nausea, and vomiting to mild attacks

of gaseous indigestion occurring after large meals. The chief characteristics are the intermittent nature of the spells and the site of pain in the upper part of the abdomen. They may be followed by scleral or generalized jaundice, or the urine may be dark and smoky, and the stools light colored. If there is infection in the biliary tract, fever, chills, and leukocytosis will be present. Such inflammation is nearly always associated with calculi, and if these produce objective signs, the nature of the disease in the upper part of the abdomen may be identified. Individual variation in the recognition of threshold pain in

TABLE 2  
CASES WITH PREVIOUS OPERATIONS ON BILIARY TRACT

	Benign stricture of the common bile duct	Stone in the common bile duct
Preoperative (original operation)		
Attacks of colic	41	40
Jaundice	21	27
Postoperative		
Attacks of colic	22	35
Relatively painless onset of jaundice	27	10
Atypical pain	8	
Original operation		
Cholecystectomy	40	21
Cholecystostomy*	9	24
Choledochostomy	6	28
Jaundice or biliary fistula**		
Immediately	35	24
Later (number and average time)	16 7.5 mo	21 3.67 yr
No colic at any time	7	2
Total	49	45

\*Several patients had had multiple operations.

\*\*Cases are included in this group in which closure of a biliary fistula was followed by jaundice.



various cases may partially explain this situation

In a few cases the colicky pain was always noted at the left costal margin or in the epigastrium with constant radiation to the left, even as far as the left scapula. There were six cases of this type, but the left-sided colic, of itself, did not indicate the type of disease present

*Pain of a dyspeptic nature*—A varying degree of indigestion may be present with a history of colic, either typical or atypical. This may be periodic or constant and for purposes of discussion will be classified as gaseous or ulcerous in type. The gaseous type is as a rule that usually associated with uncomplicated cholecystitis

A certain number of the patients complained of an ulcer type of dyspepsia, the number is surprisingly small, however, in contrast to the view sometimes expressed that there is an association between cholecystitis and ulcer, and to Bollman's experiments on animals in which he showed that in a high percentage of dogs with obstruction of the common bile duct acute ulcers developed. Such ulcers are relatively chronic. In nine of the group of cases in which operations had not been done on the biliary tract, the clinical diagnosis of associated ulcer was suggested, in each of which roentgenographic evidence was positive. In five of these cases the lesion was demonstrated at operation, in one case, the patient continued to have symptoms of ulcer after operation, although the jaundice was relieved by the removal of the stone from the common bile duct. In one case, the diagnosis was

made by the roentgenogram alone and was not confirmed by operation, in one case the surgeon noted slight edema about the duodenum but true ulcer could not be demonstrated, and in one in the head of the pancreas with a crater adherent to the duodenum, this case is the only one in the series in which the jaundice may have been due to peptic ulcer obstructing the common bile duct. A few cases presented rather atypical but somewhat suggestive histories of ulcer, but in the absence of laboratory confirmation, the diagnosis was not made, and the surgeon did not find gastric or duodenal lesion at operation

In twenty-six postmortem examinations of subjects with obstructive benign lesions of the biliary tract, only two had chronic peptic ulcer (both duodenal), neither of which was related to the jaundice. Two other subjects had had acute ulcers. In seventeen postmortem examinations of subjects with obstructive malignant lesions, only one had peptic (duodenal) ulcer. Although this had nothing to do with the cause of jaundice, it happened to be the direct cause of the patient's death by gastro-intestinal hemorrhage. In two other cases of malignant obstruction ulcers were present which were not peptic but a part of the malignant process. In the twenty-six cases, the histories usually suggested long-standing cholecystic disease. In forty-three postmortem examinations on jaundiced subjects the incidence of peptic ulcer was found to be lower than in such examinations performed as a routine

*Constant or boring pain*—The constant or boring type of pain is most

frequently encountered in malignant conditions, although it is noted in cirrhosis, certain other types of intrahepatic disease, pancreatitis, and cholecystitis with stones. In carcinoma of the pancreas it may be severe, seriously disturbing sleep, and not responding to any method of relief other than by opiates. It is usually progressive, and may be referred to the back. In some instances, jarring aggravated the symptoms considerably and was a major complaint of the patient.

*Miscellaneous associated pain*—In a few cases various types of distress occurred in the abdomen associated with exacerbations of disease of the biliary tract. Two instances are recalled in which a definite attack of "mucous colitis" occurred with each exacerbation of cholangitis following repair of stricture of the common bile duct. Physicians occasionally overlook these associated symptoms.

### PAINLESS JAUNDICE

Jaundice of painless onset frequently presents difficulty in diagnosis. If patients are young, the condition may be considered on a toxic or infectious basis, particularly if it develops during an epidemic. In later years, there may be associated symptoms such as a palpably distended gallbladder, a liver containing hard nodules, or evidences of a malignant lesion elsewhere in the body which aid in clarifying the diagnosis. Evidence of a free flow of bile into the duodenum is of value in diagnosis of many of these cases. If the gallbladder has been removed the later development of painless icterus suggests cicatricial stenosis of the common bile

duct. However, in spite of all the information that can be accumulated about these cases there are a certain number in which a satisfactory clinical diagnosis cannot be made and in those cases in which the general condition is satisfactory and in which the icterus does not show a tendency to disappear in a reasonable time the advisability of exploration must always be considered. In some cases, however, pain develops later, and this aids materially in the treatment of the patient.

The onset of jaundice was painless in 107 cases and the jaundice was due chiefly to benign strictures, pancreatic enlargements, malignant lesions of the biliary tract, intrahepatic disease, and a moderate number of calculi in the common bile duct. In a considerable number of malignant cases pain developed later.

### STONE IN THE COMMON BILE DUCT

Colic is the most significant single factor in the history of stone in the common bile duct. From a clinical standpoint, if patients are jaundiced and give a history of colic, gaseous dyspepsia, and qualitative food intolerance, one is reasonably certain in making a diagnosis of stone in the common bile duct. As has been mentioned, colic due to gallstones may occasionally be felt entirely in the left upper quadrant, with radiation, if at all, to the left side of the back, and occasionally other pathologic processes will give a similar syndrome.

We have divided these cases of stone in the common bile duct into those in which operations have been performed on the gallbladder or biliary tract, and

those in which operations have not been performed

Of the fifty-nine cases of stone in the common bile duct with jaundice in which operation had not been performed, recent colic had occurred in forty-five and remote colic (more than one month previous to jaundice) in forty-nine. In most of the cases many attacks had occurred, usually extending over a period of two to three years, in many of the cases, however, the attacks had existed for a longer period even as long as thirty years. Atypical pain varied in degree, character, and situation, and was frequently associated with colic, it was the chief discomfort in eight cases. Dull epigastric discomfort or aching in the right upper quadrant occurring intermittently or continuously, at times associated with anorexia, nausea, vomiting, and gaseous discomfort, were the chief types. Occasionally the production of symptoms by jarring or the presence of constant soreness was the chief complaint. In nine of the cases of this group jaundice developed without previous pain. The average age of the patients was sixty-four years, the youngest patient was aged fifty years. One patient had had colic after four months of painless jaundice and then the jaundice began to clear rapidly. In each case the obstruction was due to one or more large stones, the smallest being 1 cm in diameter and the largest 10 cm long and 8.5 cm, in circumference. Some of the stones were not actually in the common bile duct, but were lodged in the cystic duct or gallbladder and occluded it by pressure from without. In most cases the con-

dition was diagnosed preoperatively as carcinoma of the pancreas.

In the forty-five cases in which one or more operations had been performed on the biliary tract (table 2), recurrent typical colic had occurred in thirty-five and a definite history of stones having been found at previous operation was given in thirty-seven. In twenty-one cholecystectomy had been performed, in twenty-four cholecystostomy and in eighteen the common bile duct had been opened. In several cases cholecystostomy had been done on more than one occasion and in some cases cholecystectomy had been preceded by cholecystostomy. The patients had had stormy postoperative courses. Chills and fever were common, as were persisting biliary fistulas, when the fistulas closed pain, usually colicky, chills, fever, and jaundice were present. One or all of these symptoms occurred and promptly disappeared on reestablishment of the fistula. The onset of jaundice was relatively painless in ten cases, although in six of these there was a history of colic prior to the original operation. In two cases there was no colic, and relatively little pain. In general, the jaundice came on at longer intervals after the first operation than in cases of stricture of the common bile duct, except in the presence of persisting jaundice or of persisting biliary fistula. In cases of intervals of freedom from symptoms, the relief extended from a minimum of a few months to twenty-three years, with an average interval of three years and eight months. Attacks were often multiple, the jaundice was often fluctuating, and the laboratory data and

the physical condition of the patient, except for the fistulas, correspond to those in the cases in which operation was not performed. The surgeon reported dilated gallbladders in five cases, two, at least, being unexplainable except by the stone. Most of the ducts showed various degrees of dilatation. There were varying degrees of infection, fibrosis, and adhesions throughout and about the biliary system.

Jaundice was frequently the symptom which induced the patient with stone in the common bile duct to seek relief. A considerable number of patients had had more than one attack, lasting from one or two weeks to several months. The pain was usually fluctuating and frequently disappeared at the time the patient was examined or while under observation. The intensity of the icterus also varied considerably. Frequently it was mild, the serum bilirubin varying from 2 to 5 mg. On admission, serum bilirubin of 10 mg. was not uncommon, but in a few days a decided decline occurred. Occasionally the icterus was intense, the serum bilirubin being 15 to 20 mg., but this occurred chiefly in cases of large stones, painless onset or with associated extensive biliary cirrhosis. Duodenal drainage if done, usually resulted in a fairly good flow of bile.

In cases of stone in the common bile duct, chills and fever usually indicate infection. Diarrhea is rare and, when present, bile in the intestinal tract seems to be absent. The liver was often slightly enlarged and tender, and tenderness in the region of the gallbladder was frequently noted. There were six cases (in fifty-nine) in which the surgeon described a distended gallbladder.

In no case was this noted by the clinician. The surgeons reported a predominance of contracted, infected gallbladders filled with stones and varying degrees of infection and fibrosis throughout the biliary tract.

#### CONDITIONS SIMULATING STONE IN THE COMMON BILE DUCT

Conditions simulating stone in the common bile duct may be listed as follows: (1) cholecystitis with stones, (2) colic following cholecystectomy, (3) cholangitis, cirrhosis and hepatitis, and pancreatitis, (4) stricture of the common bile duct, and (5) malignant lesions of the pancreas or biliary tract.

*Cholecystitis with stones*—Hartman studied a group of cases of surgical cholecystitis with or without stones. In 652 cases of cholecystitis with stones a history of jaundice occurred in 207 (31.7 per cent) and in only forty-one of these was a calculus demonstrated in the common bile duct. In 375 cases of cholecystitis with calculus jaundice occurred in sixty (16 per cent). Jaundice occurred only twice as frequently when stones were present as when none were present.

In this series there are twenty-five cases of cholecystitis with stones and jaundice in which obstruction could not be demonstrated in the common bile duct. Colic occurred in fourteen cases; in one case the pain was atypical, always radiating to the left. In eight cases the onset of icterus was without pain. In two cases an ulcer type of dyspepsia had been present for seven years; in one case often with belching, nausea, and emesis. Atypical pain consisting of momentary "catching" at the

right costal margin preceded the icterus in one case. The jaundice varied in intensity. In seven cases the serum bilirubin was more than 10 mg. The icterus was of relatively short duration as a rule, a few days to two or three weeks. The clinical diagnosis most commonly made was stone in the common bile duct, but this was not demonstrable at operation. The explanation of the jaundice in this group of cases is in some respects unsatisfactory, but infection in the biliary tract extending to the finer bile canaliculi and leading to obstructive cholangitis or a toxic condition of the polygonal cell of the liver is the most reasonable hypothesis. In a few cases a large stone in the cystic duct compressed the common bile duct and led to the development of icterus.

*Colic following cholecystectomy*—It has long been known that persistent colic follows cholecystectomy in a certain number of cases. Judd and White have emphasized the part played by residual infection of the common bile duct (cholangitis) as an explanation and have advocated prolonged surgical drainage of the duct as an efficient therapeutic procedure.

*Cholangitis, cirrhosis and hepatitis, and pancreatitis*—Judd and McIndoe recently stressed the primary nature of cholangitis in some cases. This may progress, become an obliterating process, and give the syndrome of stricture in the common bile duct with jaundice. Again it may progress upward into the liver and lead to hepatitis or cirrhosis. In another group of cases jaundice occurs, and exploration reveals various pathologic processes. The surgeon may have difficulty in examining the com-

mon bile duct, occasionally feeling that a calculus may have been pushed into the duodenum. In a certain number of cases cholangitis is the chief lesion; in others extensive pancreatitis, hepatitis, or cirrhosis is the predominant lesion. In an occasional case early pancreatic or ampullar neoplasm may be present. Often these lesions are present in various combinations. They rarely occur as isolated lesions.

In this series the lesion could not be entirely localized in thirty-eight cases. Colicky pains occurred in more than 40 per cent of the cases and jaundice often recurred repeatedly. Chills, fever, and sweats were not uncommon. Atypical pains occurred at times and in some cases pain developed later. Stone in the common bile duct was the usual clinical diagnosis in this group, but in a considerable number cirrhosis of varying types seemed the likely condition from a preoperative standpoint. Cases of cirrhosis with intermittent or persisting jaundice occur, presenting repeated attacks of colicky pain suggesting stone in the common bile duct, but at exploration calculus is not encountered. A number of such cases occurred in our series. In cases of longstanding obstruction of the duct, usually from stone or stricture, considerable cirrhosis may be present and militate against the otherwise satisfactory surgical treatment of the patient. However, remarkable reparative changes can occur in the liver, we have seen several such cases. In general the results of removal of stone from the common bile duct are very favorable in spite of the extensive cirrhosis occasionally noted.

*Stricture of the common bile duct* — There were forty-nine cases of postoperative stricture of the common bile duct, in all but one of which cholecystectomy had been performed. In half of the cases painless jaundice developed, in twenty-two typical colic, and in eight atypical pain. In many of the cases jaundice or persisting biliary fistula developed immediately after operation. In the remainder of the cases convalescence was satisfactory as far as is known, but jaundice of varying degrees developed, painless, with colic, or with atypical pain, on the average of about seven and a half months after the original operation. The longest postoperative period before recurrence of jaundice was two years. It is often impossible to distinguish stricture from stone in the common bile duct but a fairly definite opinion can often be ventured by considering (1) the type of previous operation, stricture of the common bile duct practically never following cholecystostomy, (2) the length of time after operation before jaundice develops, two years or more, favoring the diagnosis of stone, and (3) the pain factor, the incidence of painlessness being much higher in cases of stricture than in cases of recurrent stones (55 and 22 per cent, respectively). In some cases in this group the surgical diagnosis was established by inference only, the adhesions were so dense and technical difficulties so great that the common bile duct could not be isolated. The part played by surgical trauma and by infection in the production of such strictures has long been debated. In our cases most of the strictures occurred postoperatively and operation

was either cholecystectomy, choledochostomy, or both. This suggests that trauma must be a significant factor. In all these cases, however, varying degrees of infection were present at the time of operation. There were also a few cases in which obliterative cholangitis is found at operation or necropsy. In these cases the ducts were reduced to fibrous cords, presumably as the result of long-standing infection, and the cases were invariably associated with considerable cirrhosis. The following case of stricture occurring after cholecystostomy may belong to this group.

A woman, aged forty-three years, had had cholecystostomy in 1923 following a two-year history of colic, and jaundice of six weeks' duration immediately preceding operation. The jaundice cleared, drainage ceased after eighteen days, and the patient was reasonably well for a year. Following this, she had recurring attacks of colic with jaundice of one to three months' duration. Operation in 1926 showed "obliteration of the common duct from the cystic duct to duodenum, forming a fibrous cord. The right upper quadrant was a mass of adhesions." Cholecystenterostomy was done. The subsequent course was reasonably satisfactory for a time, but clinical evidences eventually developed of cirrhosis, recurrent gross gastric hemorrhages, enlarged liver, and slightly elevated serum bilirubin with a direct van den Bergh reaction, suggesting that the infectious process had progressed up into the liver.

Although colic often is one of the prominent symptoms of stricture, its presence followed by icterus which clears in a short time, always raises the question of the presence of calculus. Moreover, it is unusual to find the two conditions associated. A certain degree of cholangitis is frequently present and may be the basis of the attacks.

of colic, chills, fever, and icterus that occasionally occur after plastic repair of structure. The fact that calculi may be the basis for such attacks and should always be considered, is illustrated in the following case.

A man, aged forty-one years, was first seen in April, 1927. Three months previously he had had an acute gangrenous appendix removed. After a month he began to suffer from biliary colics and cholecystectomy was done. The gallbladder was found to contain multiple stones. Five days post-operatively slight icterus appeared followed by discharge of bile from the wound. This condition persisted. Later pain in the abdominal wall near the wound, malaise and fever developed. Drainage of a superficial abscess was performed.

On examination there was evidence of a biliary fistula and abscess of the abdominal wall. Serum bilirubin was 2.3 mg and test of hepatic function by the dye method showed retention, graded 3. Further drainage of the abscess in the abdominal wall was necessary on two occasions, following which the infection cleared, but the fistula persisted. July 18, 1927, the fistula was explored and was found to lead into the hepatic ducts. Signs of the distal duct were not discoverable. Hepaticoduodenostomy was performed for the stricture. Shortly after the patient was dismissed, colic, chills, fever, jaundice, and vomiting developed and persisted until his return in July, 1928.

Examination was satisfactory except for slight icterus and a ventral hernia. Exploration was again thought advisable, but the anastomosis appeared in good condition. Extensive adhesions about the liver, the parietal peritoneum, and the intestines were separated, and the ventral hernia was repaired. Symptoms recurred after the patient's dismissal and progressed, leading to loss of weight and general decline in health. On his return there was icterus and slight enlargement of the liver. Exploration was again undertaken. The ducts were found packed with stones. These were removed and a T-tube inserted for prolonged external drainage. The anastomosis again appeared

to be in good condition. Convalescence was excellent and the patient gained remarkably in weight and strength.

*Malignant lesions of the pancreas or biliary tract.*—With carcinoma of the pancreas pain is a common symptom and may or may not be associated with jaundice. Mussey and Eusterman reviewed different groups of cases observed at The Mayo Clinic. Pain of various types may be present for several months before further symptoms present themselves or it may be a late development. Jaundice may be the first symptom or it may not occur until late in the course of the disease. Its presence or absence probably depends on the site of the malignant lesion in the pancreas and possibly on the degree of any associated infection. If the head of the pancreas is involved jaundice usually occurs early whereas if the tail or body is primarily involved, it occurs much later and pain is an earlier and more prominent symptom. Careful study of the type of pain and the time of onset may give valuable assistance in the diagnosis. In our series of thirty-eight cases the onset of jaundice was painless in nineteen cases, but pain occurred prior to the onset of jaundice in fourteen cases. In eight cases there was colic and in six cases other forms of pain were present. In most of the cases pain persisted after the onset of jaundice and in some cases of painless onset, pain developed later. It is also probable that pain occurred later in the course of the disease in many cases.

We do not suggest that pain with carcinoma of the pancreas is uncommon, two-thirds of our patients suffered pain of considerable degree dur-

ing the course of their illnesses. However, it should be noted that the onset of jaundice was often painless (50 per cent) and that when pain was present it was frequently atypical as compared to that of biliary colic, although such typical colic occurred in five cases.

Except in cases of colic, the pain was for the most part different from that encountered with stones. There was less variation, less tendency to occur in attacks, and it was usually described as a constant dull aching or boring distress often seriously disturbing sleep. The pain was described as occurring in the middle portion of the epigastrium, in the left upper quadrant, to the left of the naval, or in the left portion of the epigastrium. In later stages, after the development of jaundice, more or less constant pain, often extending into the back and into the region just posterior to the pancreas, is common.

Other diagnostic aids may be noted. The average age in our cases was fifty-six years. Fever occurred practically as frequently as in cases of stone in the common bile duct. Diarrhea occurred in six cases, all before the onset of jaundice, suggesting obstruction of the pancreatic duct prior to involvement of the common bile duct. There was a history of more than one attack of jaundice in only one case. A single attack of jaundice, usually of a stationary or progressive type with relatively high serum bilirubin (10 to 35 mg for each 100 c c) and absent (or scanty) flow of bile through the duodenal tube, is the rule. A distended gallbladder was reported by the surgeon in thirty-four cases and was felt by the clinician in twenty-four cases. An enlarged

liver was frequently palpated and there was slight tenderness in the right upper quadrant. In only six cases did the surgeon observe metastases, in all cases these were in the liver.

Primary carcinoma of the ducts or ampulla occurred in nine cases. In seven of the cases the onset of jaundice was painless. In one case there was atypical pain with radiation to the left, and in one case there was colic. In general, such cases may be compared with cases of carcinoma of the pancreas, as regards history, and general and laboratory data, often a distinction cannot be made.

There were five cases of primary carcinoma of the gallbladder. Exploration only was done, and consequently the incidence of gallstones could not be accurately estimated. They were found in one case in which colic had been present for many years. In one case colic had been present many years previously. In the other three cases the symptoms began with painless jaundice. The actual cause of jaundice in these cases is usually extension of the malignancy to the common bile duct.

There were seven cases of metastatic carcinoma of the liver, primary in various organs, chiefly the stomach. In such cases, the jaundice is relatively painless in onset, but later may be associated with more or less constant pain in the right upper quadrant or back. It must always be remembered that relatively painless jaundice may be due to secondary carcinoma of the liver with a silent primary growth elsewhere and careful search for such growth should not be omitted.



## SUMMARY

Although colic is the most typical pain in disease of the biliary tract and when associated with jaundice is usually indicative of stone in the common bile duct, yet it may be absent or replaced by equivalents of much milder degree. The intermittency of symptoms and their site in the upper part of the abdomen, and the association of evidences of infection are valuable features in localizing the disease process. Moreover, typical colic may occur in other conditions and the total symptoms may simulate calculus of the common bile duct to a large extent and lead to erroneous diagnosis. Such conditions are cholecystitis with or without stones and without evidence of stones in the common bile duct, colic following cholecystectomy, stricture of the

common bile duct, cholangitis, carcinoma of the pancreas or biliary tract, and cirrhosis. Thus, although colicky attacks had occurred in approximately 80 per cent of the cases of stones in the common bile duct in which operation had been performed, they had also occurred in approximately 45 per cent of cases of stricture and in 13 per cent of cases of carcinoma of the pancreas. On the other hand, pain may be absent in relation to the onset of the jaundice in many of these conditions. Thus jaundice developed with relatively no pain in 50 per cent of cases of carcinoma of the pancreas, in 55 per cent of the cases of stricture of the common bile duct, in 14 per cent of the cases of stones in the common bile duct, and in 22 per cent of cases of stone in the common bile duct in which operation had been performed.

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# Appendiceal Oxyuriasis\*

## A Study of its Incidence in 20,969 Extirpated Appendices

By HAROLD GORDON, M D, *Ann Arbor, Michigan*

THE incidence of appendiceal oxyuriasis and its etiologic rôle in the evolution of appendicitis have been subjects of widespread medical interest. In this paper, only the incidence of oxyurids in the appendix is considered, their etiologic significance being the subject of a separate communication. The present study is unique in so far as it supplies figures for a larger series and one collected over a longer period of time than any previously reported.

### LITERATURE

Since Still<sup>45</sup> and Metchnikoff<sup>28</sup> first drew serious clinical attention to the subject, intestinal helminthiasis has been responsible for many reports. Notwithstanding the many studies already made, a fairly comprehensive review of the literature reveals a striking variation in the figures submitted for the incidence of appendiceal oxyuriasis. This holds true as well for the same as for different countries. In England, Still<sup>45</sup> reported oxyurids present in 38 of 200 consecutive autopsies on children under 12 years of age. Of this number, 25 showed parasites both in the cecum and in the appendix, 6 in the

appendix only, and 7 in the cecum alone. In a second series of 100 necropsies on children between the ages of 2 and 12 years, 32 were positive for threadworms. The number of times the appendix was implicated in this series is not stated<sup>46</sup>.

Eastwood<sup>14</sup> examined 123 appendices—73 operative and 50 post mortem specimens—and found oxyurids in 14 of each group. Innes and Campbell<sup>22</sup> found oxyurids in 17 of 100 extirpated appendices. Rendle Short<sup>41</sup> found "oxyurid appendicitis quite common," but does not submit exact figures of its incidence. For Great Britain, therefore, the total reported incidence is 97 in 523 appendices examined (18.5%).

In France, Brumpt<sup>6</sup> and Railliet<sup>31</sup> made extensive studies. Brumpt<sup>6</sup> noted oxyurids in 35.4% of 800 autopsies. In Broca's service threadworms were seen in 10 of 27 appendices<sup>6</sup>. Railliet<sup>31</sup> found threadworms in 14 of 33 appendices and again in 58 of 119<sup>6</sup>. This yields a total incidence of 11.9% for 800 autopsies and 179 surgical specimens.

The German literature is especially rich in studies on the incidence of oxyurids. Suzuki<sup>47</sup> investigated material from 500 autopsies and 103 appendectomies. Of the former, 38 showed

\*From the Department of Pathology, University of Michigan, Ann Arbor, Michigan

oxyurids in the cecum and appendix, or in the appendix alone, while 6 harbored the parasites in the cecum only. The operative material contained parasites in 16 instances. Fischer<sup>10</sup> found oxyurids in 46 of 110 extirpated and in 29 of 105 post mortem appendices. Steichele<sup>41</sup> reported two series; in the first series of 1023 appendectomies, oxyurids occurred 17 times, in the second series of 234 operations, 24 times.

Jaroschka<sup>24</sup> made a study of 148 surgical specimens and found pinworms in 28. Nicolaus<sup>30</sup> found oxyurids in every one of 5 appendices removed at operation. Aschoff<sup>1</sup>, in one series, found oxyurids in 14 of 78 specimens, in another series only twice in 1000 specimens<sup>2</sup>. Serbinow and Schulmann<sup>40</sup> examined scrapings from the peri-anal folds and from the anal and rectal mucosa of asylum children. Their subjects ranged in age from a few months or less ("lying infants") to 4 years. They were able to demonstrate threadworms or their ova in 4 of 25 "lying infants", in 8 of 11 "creeping infants", and in 54 of 77 children aged from 1 to 4 years. Using the same method of repeated scraping at intervals, one of the authors<sup>40</sup> demonstrated the presence of oxyurids in 84.5% of 117 farmers and peasants aged from 23 to 25 years.

Japha<sup>28</sup>, using a special glass spatula, found oxyurids in scrapings from 132 of 200 school children suspected of harboring intestinal parasites (66%). On another occasion he examined a group of 285 unselected school children and found oxyurids in 209 (73%). The same author cites the following figures of other investigators, viz. Berndt, in Jena, examined 1000 child-

ren and noted oxyurids in 76%; Goebel, in the same city, 44.6% of 1000 children; Bank, in Munich, 30.6% of 315 children; Ruotsalainen, in Finland, 31.7% of 300 children; Gottberg, in Bonn, 32% of 200 children, and Hage, 8% of 300 adults from a German rural community examined during a typhoid epidemic. That these figures would equally well hold true for the appendix itself, can hardly be proven. Yet the fact that Still<sup>42</sup>, Suzuki<sup>17</sup>, and Rheindorf<sup>33</sup> found the appendix usually implicated when the parasites were present in the intestinal tract, makes reasonable the assumption that the appendix would be involved in the great majority of the above instances.

Rheindorf<sup>32, 33, 34, 35</sup> found oxyurids in 62% of 13 extirpated appendices and in numbers varying from as low as 5% to as high as 45% at autopsy, depending upon the age incidence of the hosts. Lawen and Rheinhardt<sup>20</sup>, in Leipzig, found 9.8% of 620 extirpated appendices positive for the presence of oxyurids. Heller<sup>20</sup> noted oxyurids in the intestine in 23% of 611 autopsies and in "most of them the oxyurids were also present in the appendix". Baarnhielm<sup>8</sup>, in Sweden, during the period May 1, 1905, to December 31, 1912, found 77 of 875 extirpated appendices positive for the presence of threadworm (11.3%). Brauch<sup>5</sup> found oxyurids in 55% of "normal" appendices examined at autopsy and in 2 of 25 surgical specimens exhibiting acute inflammation (8%). Druener's<sup>18</sup> figures are 48% for post mortem material and 8 of 86 acutely inflamed appendices (9%).

Liengme<sup>27</sup> noted oxyurids in 7 of 159 appendices showing acute inflam-

mation (4%) Riff<sup>86</sup>, in Strassburg, found pinworms in 32% of 152 surgical specimens Sagredo<sup>88</sup> examined 100 appendices removed at operation and found parasites or their ova in 41 On the other hand, Hoffman found oxyurids in only 19 of 4000 extirpated appendices, Seiffert none in 2000, Moschowitz none in 2000, and Retzlaff none in 600<sup>88</sup> In summary, then, the reported incidence of appendiceal oxyuriasis for continental Europe ranges from 37% for 13,522 surgical to 16.5% for 2416 autopsy specimens But if we include also the figures for intestinal oxyuriasis *in vivo*, we obtain an aggregate incidence of 14.7% for 19,768 appendices and even this figure is probably a conservative reflection of the actual incidence

Statistics for the North American continent are not nearly so plentiful Cecil and Bulkley<sup>8</sup> examined 148 unselected appendices of children between 2 and 15 Their series was made up of 129 surgical and 19 autopsy specimens They found oxyurids in 3 of the necropsy and in 17 of the surgical cases They also noted oxyurids in 4 appendices removed from adults Harris and Browne<sup>19</sup> found threadworms in 22 of 121 consecutive appendices received for routine diagnosis Garlough<sup>17</sup> recorded 4% positive for pinworms Schloss<sup>39</sup> made a careful study of the incidence of helminthiasis in children from New York's East Side His subjects, ranging in age from 2 to 12 years, were divided into two groups The first group comprised 30 subjects complaining of symptoms suggestive of helminthiasis Twelve members of this group harbored parasites or their ova The second group,

made up of 280 unselected children, exhibited oxyurids in 22 instances The author felt, however, that his figures failed to reveal the true incidence, since he had to content himself with single examinations of small stool specimens, and it is an accepted fact that a single negative stool examination is not conclusive

Erdmann<sup>15</sup>, during the two year period, January, 1902, to December, 1903, removed 201 appendices; 22 of these came from children under 10, complaining of acute symptoms and of this number 4 contained oxyurids Crile<sup>9</sup> fails to record the finding of a single oxyurid in 1000 appendectomies Ney<sup>29</sup> found oxyurids in 3 of 100 appendices removed at operation Hanley<sup>18</sup>, reporting an appendix filled with threadworms, says it is the first he had seen in 500 operations Deaver<sup>10</sup> found oxyurids once in 500 appendectomies on children, while Deaver and Ravdin<sup>11</sup> noted oxyurids in not quite 1% of another series Stiles and Garrison<sup>44</sup> examined the feces of 123 children under 15 years of age and found oxyurids in 2 instances Castellani<sup>7</sup> quotes Garrison's figures for the incidence of oxyuriasis in the Philippine Islands (8%) and Dobson's figures for India (15.37%) Wood<sup>51</sup>, in Australia, reported oxyurids present in 7 of 57 extirpated appendices These statistics suffice to show that appendiceal oxyuriasis occurs the world over, though with varying frequency

#### MATERIAL AND METHODS

The present series consists of 20,969 appendices received for routine diagnosis at the Pathology Laboratories of the University of Michigan during

the period July 1, 1894, to December 31, 1930. Only surgical specimens have been included. As will be shown, autopsy specimens are not necessary as controls. A few specimens received in an unfixed or dried up condition, are not included. The bulk of the material under review was derived from residents of Michigan, although a small proportion was sent in from neighboring and even from distant states. A part of the material was removed in hospitals of outlying cities and towns, the remainder at the University Hospital. The entire series, made up as it is of unselected specimens from patients of both sexes, all ages, urban and rural communities, represents an excellent cross-section of the appendices of this state.

The appendices were received ready fixed in a 10% aqueous solution of formol. After being examined grossly, they were cut into small blocks for paraffin impregnation. Staining was done with hemalum and eosin by the celloidin sheet method. During the past 23 years the blocks have been routinely selected to include representative portions of the proximal, mesial, and distal thirds of the appendix. Prior to 1908 the organs were sectioned at one or two points only. Duplicate sections were made in every case. Serial sections were not attempted since the material was received for routine microscopic diagnosis. However, the very size of the series tends to distribute the possible errors of the method and renders the study of statistical significance. In this connection, it is of interest to record that when oxyurids were found, they occurred in groups of considerable numbers, so

that while one block often showed a marked numerical preponderance of the parasites, the other two blocks seldom were completely devoid of worms. Numerous workers have commented upon a similar grouping of the parasites, Still<sup>45</sup> finding them most frequently in the proximal, other writers nearer the distal third. The diagnosis for the entire series, with few exceptions, were made by Dr. A. S. Warthin in person, the writer being privileged to have access to the files. In no instance was an opinion recorded by other than experienced assistants.

#### RELATIONSHIP TO AGE AND TO SEX

In Table 1 is recorded the distribution of the positive appendices, arranged according to the age and sex of the hosts. Of the 20,969 appendices examined, 221 contained oxyurids (1.05%). Calculated for each sex, the percentage incidence is 1.26% for females and .74% for males. Even allowing for the larger number of appendices received from female patients, the percentage figures show a significantly higher incidence in female than in male patients. This holds true even when we contrast the absolute and percentage incidence figures for the two sexes where the ages are given. Thus, during the age period of 2 to 46 years, 6106 appendices received from female patients revealed oxyurids in 86 instances (1.4%), while 3690 appendices received from male patients contained oxyurids in 37 instances (1%). The increased frequency of oxyuriasis in females may have some bearing on the mode of infection. Several authors (Fisher<sup>16</sup>, Steichele<sup>43</sup>, Ssolowjew<sup>42</sup>, Wilhelm and Quast<sup>50</sup>, and Harris and

TABLE 1

Age Groups	Males		Females		Both Sexes		Sex not Stated	Total Appendices
	Total	Oxys	Total	Oxys	Total	Oxys		
Not Stated	3307	16	6555	80	9862	96	324	10,186
0-23 Mos	5	0	2	0	7	0	1	8
2-6 yrs	99	9	74	6	173	15	4	177
7-11 yrs	226	10	237	12	463	22	4	467
12-16	374	6	701	21	1075	27	0	1075
17-21	797	3	1375	12	2172	15	13	2185
22-26	732	2	1191	12	1923	14	12	1935
27-31	552	5	915	9	1467	14	4	1471
32-36	404	1	726	4	1130	5	5	1135
37-41	297	1	500	6	797	7	2	799
42-46	209	0	387	4	596	4	6	602
47-51	158	0	245	0	403	0	10	413
52-56	98	0	147	0	245	0	2	247
57-61	54	0	81	0	135	0	0	135
62-66	37	1	45	0	82	1	0	82
67-71	15	1	18	0	33	1	0	33
72+	12	0	6	0	18	0	1	19
TOTAL	7376	55	13205	166	20581	221	388	20969

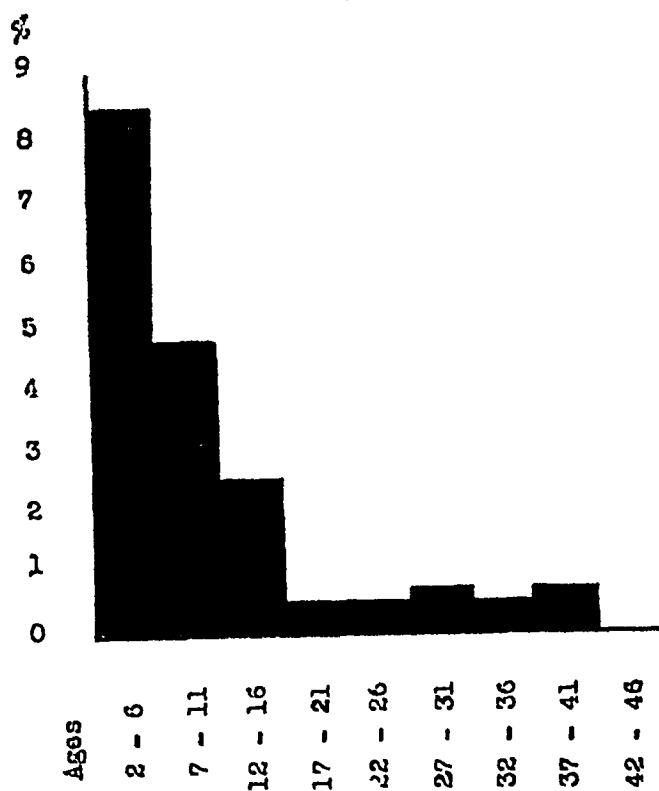
Age and sex incidence of oxyuriasis of all patients, calculated at 5 year periods

Browne<sup>19</sup>) have recorded similar results, though a few authors have reported a slightly higher incidence among male patients

The relative frequency of oxyuriasis in the two sexes is related also to the age incidence of the hosts. In this study the age groups are recorded for five year periods. These periods have been selected to correct for the well-known tendency of patients to "favor multiples of five and, in lesser degree, the even years in giving their ages" (Weller<sup>49</sup>). In Table 1 we note that where the ages are stated, the highest incidence of oxyuriasis occurs during the age period 12-16, with the age period 7-11 in second place numerically. The total incidence for the various age groups, however, hardly reveals the true facts, because of the great variation in the number of appendices received from each age group. To correct for the discrepancy in numbers, in Table 2, the percentage incidence of oxyuriasis has been calculated for each

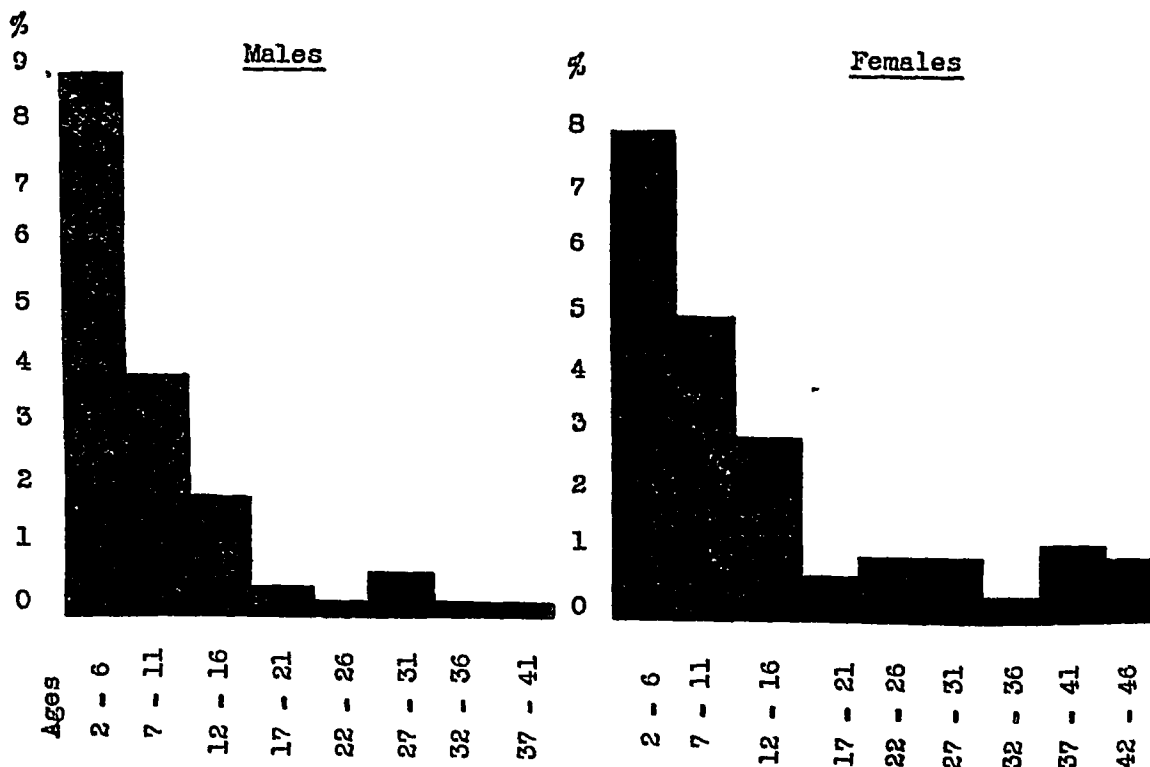
group and plotted in the form of a graph. Stated in this manner, the relationship between the age of the host and the occurrence of oxyuriasis becomes immediately apparent. Thus, from a peak of 8.5% during the age period 2-6 years, there is a rapid decline to 4.7% during the second half of the first decade, with a further fall to 2.5% for the period 12 to 16 years. From the 17th to the 46th year the percentage incidence varies but little, while after the 46th year appendiceal oxyuriasis is almost unknown in Michigan. These findings are once again in accord with previously reported studies. Comparing the sex and age percentage incidence figures (Table 2a) we find that oxyuriasis is persistently more frequent in females than in males after the 6th year, with a much less abrupt decline for the three five year periods from the 2nd to the 16th year and with a more evenly maintained distribution from the 17th to the 46th year. As will appear later, the more frequent mani-

TABLE 2.



Percentage incidence of oxyuriasis at various age periods for both sexes

TABLE 2A



Percentage incidence of oxyuriasis at various age periods for each sex.

festation of oxyuriasis in children is probably related to the mode of infection. In passing, it is an interesting coincidence that both the oldest and the youngest case of oxyuriasis occurred in males, aged 69 and 2½ years respectively.

#### SEASONAL INCIDENCE

Inquiry into the possibility of a seasonal predilection reveals that the monthly variations in the occurrence of helminthiasis (Table 3) are not greater than can be accounted for by chance.

TABLE 3

Monthly and seasonal incidence of oxyuriasis

December	18	
January	18	
February	19	
<hr/>		55
March	11	
April	16	
May	17	
<hr/>		44
June	23	
July	16	
August	27	
<hr/>		66
September	24	
October	18	
November	14	
<hr/>		56
<hr/>		221 221

distribution and the observed fact that more appendices are received for section during the second half than during the first half of the year. Nor is the seasonal incidence sufficiently varied to be statistically significant. This phase of the problem is intimately bound up with the wider ones of the

probable persistence of infection and of an equally probable delay in the manifestation of symptoms. The frequent finding of mature forms, the occurrence, side by side in the appendix, of adult and of young worms, the occurrence of female worms filled with ova, the occasional presence of ova only, all the facts speak for chronicity of infection. It is therefore not unlikely that the symptoms, reflex and direct, are a poor index of the date of infection and much more probable that they lag far behind the initial occurrence of oxyuriasis, thus affording the parasites time to complete a greater or lesser period of their life cycle before discovery.

#### RELATIONSHIP BETWEEN OXYURIASIS AND APPENDICITIS

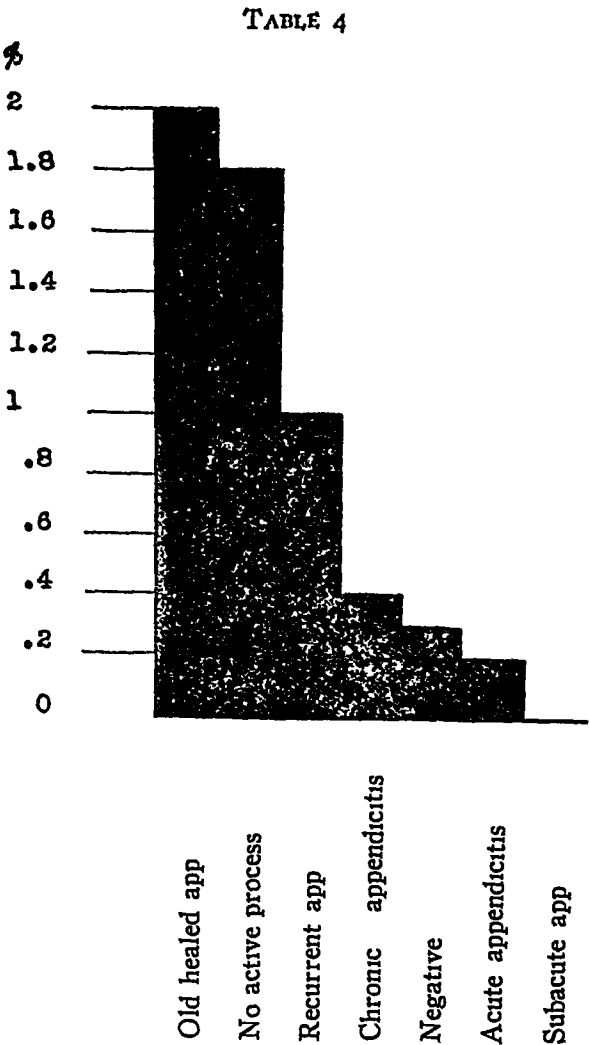
This phase of appendiceal oxyuriasis will be discussed in detail later and is here touched on only briefly. That there is a relationship between oxyuriasis and appendicitis, has been fully discussed both pro and con. The very large number of single case reports is mute evidence of the interest and significance attaching to this phase of the problem, with Rheindorf<sup>32,33,34,35</sup> and Aschoff<sup>1,2</sup> playing leading rôles in the controversy. In Table 4 is plotted the percentage incidence of oxyuriasis for each of seven types of appendices most frequently involved. This list includes not only some of the well recognized types of inflammation, but also groups of appendices whose exact place in the general pathology of the appendix may not be immediately apparent. These diagnoses are in keeping with Warthin's dictum that "a full and adequate analysis - - - - - is of more objective



value than the bare diagnosis"<sup>44</sup> Accordingly, the appendices showing hyperplasia of the lymphoid tissue, fecal concretions, dilatation of the lumen, atrophy and chronic catarrh of the mucosa, or any combination of these changes, are classified as showing "No active process" The appendices failing to show even such slight changes as listed above, are grouped as "negative." These are, to all intents, "normal" appendices A sufficiently large number of appendices of this type are included to render unnecessary

the use of autopsy material for control purposes The limitation of this study to surgical specimens introduces fewer variants and allows a more accurate analysis of the factors entering into the causation of oxyuriasis. The appendices showing an increase of connective tissue of the submucosa are grouped under the title "Old healed appendicitis," the old fibrosis constituting the only indication of the obsolete inflammation

The percentages recorded in Table 4 show a significant relationship be-



Relationship of oxyuriasis to the general pathology of the appendix

tween the presence of oxyurids and the type of appendix harboring the parasite. Oxyurids were seen most frequently in the group of appendices showing an old healed inflammation (2%) and next most frequently in those showing no active process (18%). The appendices showing evidences of recurrent inflammation were affected in 1% of their number. The chronically inflamed organs, the frankly negative, and the acutely inflamed ones show a closely similar percentage incidence, while in no instance were oxyurids found in association with subacute appendicitis. Not only do the percentage figures show a significant association between oxyuriasis and appendices devoid of active inflammation, but by actual count oxyuriasis occurs more than twice as often in the inactive appendices as in the actively inflamed organs. This finding is somewhat in line with the recorded observation that native Chinese show a high incidence of helminthiasis, yet rarely exhibit acute appendiceal attacks. Here, however, we must not lose sight of such modifying factors as a stoical disregard of pain and difficulty of access to competent surgical and diagnostic attention.

#### THE INCREASING INCIDENCE OF APPENDICEAL OXYURIASIS

The increasingly frequent observation of oxyurids in appendices received for routine diagnosis during recent years primarily was responsible for the initiation of this study. That this observation is not merely an impressionistic one is proved by the objective data furnished in Table 5. In this table are recorded the total appendices received, calculated for five year periods, from 1894-1930, with the total and percentage incidence of oxyuriasis for each of these periods. Except for the initial and the final periods, the percentage incidence is surprisingly similar. That appendiceal oxyuriasis is on the increase in Michigan can hardly be gainsaid. This is even more strikingly evident when we contrast the figures, absolute and percentile, for the two periods 1894-1925 and 1925-1930. In each case the figures are computed as from July 1st to June 30th, except for the year 1930, in which the figures up to December 31st are included. Up to June 30th, 1925, 5,572 appendices were sectioned and oxyurids were present in 23 instances (41%), while since June 30th, 1925, threadworms were present in 198 of 15,397 appendices (1.28%).

TABLE 5

Year Period	Total Appendices	Total Oxyurids	Percentage Oxyurids
1894-1900	32	0	0.00
1900-1905	304	1	.33
1905-1910	319	1	.31
1910-1915	624	2	.32
1915-1920	1817	6	.33
1920-1925	2476	13	.52
1925-1930*	15397	198	1.28
Totals	20,969	221	1.05

\*December 31, 1930

Total appendices, incidence, and percentage incidence of oxyuriasis, calculated at five year intervals, 1894-1930

Such a decided increase can hardly be attributed to coincidence and must surely be bound up with the larger problem of the usual method of infection

### COMMENT

How can this relative and absolute increase best be accounted for? At an early stage of this study an attempt was made to segregate the urban and rural cases. Such a distinction, however, is hardly valid for a state as closely settled as Michigan, and one, moreover, where an abundance of automobiles and of good roads make for a free commingling of the entire population. Therefore, whatever the cause for the increase, it can be attributed only to factors operating in town and country alike. While the past decade has seen a very considerable increase in the population of Michigan, there has been but little change in the average composition of its people. An altogether negligible number of these appendices were derived from the Detroit area or from the other large manufacturing centers. These are the areas which have seen the largest influx of aliens and the most marked rise in population. The bulk of the appendices were sent in from communities showing a steady rather than a phenomenal increase in numbers. Increased immigration can therefore not fairly be blamed for the increased incidence of oxyuriasis. Probably the biggest single change in habits during the past decade, other than those occasioned by improved methods of transportation and communication, has been in habits of diet. In earlier years, meats, cooked vegetables, dairy products, and bread furnished the staple foods. Now popu-

lar fancy, intrigued by the romance of the newly discovered vitamins, and under the urge of advertising, demands a plentiful supply of accessory food factors in the daily menu. Raw fruits and fresh vegetable salads, at one time reserved for a few educated palates, now figure prominently in the bill of fare of most homes. Improved refrigeration and marketing facilities have aided materially in increasing the consumption of leafy vegetables and fresh fruits. Thus, while the estimated population of Michigan has increased from 3,668,412 in 1920, to 4,283,860 in 1925, and to 4,591,000 in 1928, the cultivation of fruits and vegetables for consumption has in some instances doubled, in others tripled, only a few products being produced to a lesser extent during the stated periods. In addition to the increased home production of perishable fruits and vegetables, there has been an even more marked increase in the importation of such foods from other states. That this change in diet may indeed be an important etiologic factor, is indirectly attested to by the greater frequency with which seeds and coarse vegetable fibers are seen in "modern" appendices. Moreover, infection through contaminated fruits and vegetables affords a logical explanation for the observed greater frequency of oxyuriasis in females than in males, and in children than in adults. Women are more commonly concerned in the preparation of meals than men, hence more apt to come in contact with infected foodstuffs, and children are less apt to be observant about exact and careful preparation of the leafy vegetables than are adults.

The sparsely known facts of the life cycle of *Oxyuris vermicularis* do not refute the above hypothesis. Castellani<sup>7</sup> states that the threadworm is parasitic only for man. Wilhelm and Quast<sup>51</sup> demonstrated oxyurids in cockroaches and in mice, but were able to distinguish these from the human parasite by the constantly larger size of the latter. During a period of fifteen years spent in the analysis of more than a thousand samples of water, these authors were unable to find oxyurids or their ova in a single sample. They therefore do not favor contaminated water as a likely source of infection. Nor, according to the same authors, do flies act as vectors since they could find no ova on flies confined for twenty-four hours in a glass cage with infected mice. They were equally unsuccessful in implicating the dust of schoolrooms, since they were unable to find ova in the dust, even when they had previously placed some there themselves. They, therefore, incline to Leuckhardt's theory of auto-infection. This seemed to them the most likely method, as proved by their ability to recover ova from under the nails of a high percentage of infected school-children. They tested the nails of the index, ring, and middle fingers of both hands of 1000 school children and found the test highly successful even when the nails had previously been cleaned. They also showed a relationship between the percentage of successes and the ages of the subjects. Young children (class 7A and 7B) and children in the "upper class" showed a relatively low incidence of nail bed infestation, due, probably, in the former instance to parental, in the latter to personal care of the nails.

However, while this may indeed be a fruitful source of re-infection, it is difficult to conceive how it can operate in the spread of oxyuriasis from person to person.

Langhans<sup>25</sup> states that Leuckhardt's theory is now generally discredited. He found empty egg shells in the peri-anal folds and therefore concluded that the young larvae ascend along the intestinal canal. Still<sup>45</sup>, noting many immature forms in the appendix and the nearby cecum and none in the small intestine, concluded that the appendix is the selective breeding ground of the parasites. The admittedly lower incidence of appendiceal as contrasted with intestinal oxyuriasis, hardly supports such a hypothesis. Drigalski and Koch<sup>12</sup> on the other hand, found an equal incidence (59%) of oxyuriasis in 100 children whose appendices had been removed and 100 normal controls, both groups selected at random from among 21,000 school-children between the ages of 6 and 14 years. These authors relate the occurrence of oxyuriasis to the constitutional pathology of the hosts. Of the 200 children examined, oxyuriasis occurred but once in 6 pyknic (16%), in 16 of 22 asthenics (73%), and in 96 of 172 eumorphics (55%). They relate their findings to the factor of constitutional constipation, rare in the active, well muscled pyknics, common in the ptotic, more sluggish asthenics. The longer intestinal tract of the latter favors concentration of the feces, tending towards constipation. Drigalski and Koch thus argue that the oxyurids develop and multiply in situ. Steichele<sup>43</sup> in commenting upon the greatly increased incidence of appendiceal oxyuriasis dur-

ing the post-war as contrasted with the pre-war periods, suggests overcrowding, poor diet, and contamination of vegetables with excreta as the most likely causes of the increase. Bass<sup>4</sup> believes that self-infection and contamination of fruits and vegetables are the usual methods of acquiring the disease, with the further possibility that it may also be fly-borne. She states that the eggs develop only after entering the gastro-intestinal tract and being acted upon by the digestive juices. One other factor must be considered in explaining the increased incidence of appendiceal oxyuriasis. In earlier years catharsis was a routine part of the pre-operative preparation of patients, whereas now they are usually given a gentle enema. Also, while the average pre-war parent made frequent use of drastic purges for the abdominal complaints of children, the more modern mother, educated to its possible dangers, refrains from such a method of therapeutics.

## CONCLUSIONS

- 1 In a series of 20,969 extirpated appendices, oxyurids were found in 221 (1.05%).
- 2 Females are much more commonly infected than males (1.26% and .74% respectively).
- 3 Infestation is much more common during the first decade of life than in later years and almost unknown in Michigan after the 46th year.
- 4 There is no significant seasonal predilection for the occurrence of oxyuriasis.
- 5 The incidence of appendiceal oxyuriasis is significantly greater during the past decade than during the earlier years of the period under survey.
- 6 The increased frequency of appendiceal oxyuriasis is probably related to the increased consumption of uncooked leafy vegetables and raw fruits.

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# Idiopathic Thrombopenic Purpura\*

By ERASTUS I GULLER AND JOHN S LAWRENCE, *Rochester, N Y*

THE symptom-complex of idiopathic thrombopenic purpura is too well known to justify the reporting of additional patients with this disease. Atypical forms of this disorder are recognized but they have received much less attention. Accordingly it has seemed justifiable to report the five cases occurring in this paper since their data illustrate some of the atypical forms of this condition. These patients demonstrate how difficult it may be in some instances to distinguish aplastic anemia from idiopathic thrombopenic purpura. They further emphasize the fact that a marked leucopenia may be an associated finding in some of the patients with this disorder as contrasted with the usual normal or increased numbers of white blood cells.

*Case 1* S B, unit number 25861, a white, male student, was admitted to the Strong Memorial Hospital July 1, 1929, because of epistaxis, ease of fatigue and dyspnea. The onset of epistaxis was three months prior to admission. The nasal bleeding was severe and was controlled with difficulty by packing. Two similar attacks had occurred at monthly intervals. For two months he had noticed that he had bruised readily and for one month ease of fatigue and dyspnea had been marked.

The family history was irrelevant.

The past history. He had measles at 10 years of age and scarlet fever at 13 years of age. He has never developed any permanent teeth. Otherwise, the past history was negative.

Physical examination. The patient was a tall, thin, pale boy, aged sixteen years. There were no purpuric spots and no fresh petechiae in the skin. There was no general glandular enlargement. The mucous membranes were pale. There was a small petechia on the posterior pharyngeal wall. The conjunctivae were very pale. The fundi showed no hemorrhages. The nose was filled with a clear mucoid material. The nasal septum was deviated to the left. There was no evidence of blood in the nasal passages. The teeth had orthodontic appliances and were deciduous. The Rumpel-Leede test was negative. The physical examination revealed no other abnormal findings of interest.

Laboratory examinations. The total red blood cell count was 3,950,000 per cu mm, the hemoglobin was 60.0 per cent, and the total white blood cell count was 6,600 per cu mm. The white blood cell differential formula was neutrophils 72.0 per cent, eosinophils 6.0 per cent, basophils 2.0 per cent, lymphocytes 14.0 per cent, and monocytes 6.0 per cent. In a fixed smear, the red blood cells showed marked achromia, and moderate variations in shape. The platelets were considerably reduced. The reticulocyte count was 3.0 per cent and rose to 12.0 per cent while iron and whole liver were being given. The coagulation time was 13 minutes. The blood clot did not retract and was very friable. The bleeding time was 16 minutes. Nine months later the red blood cell count had risen to 4,740,000 per cu mm and the hemoglobin value had increased to

\*From the Department of Medicine, University of Rochester, School of Medicine, and the Medical Clinic of the Strong Memorial Hospital and Rochester Municipal Hospital.



900 per cent At this time, the coagulation time was 17 minutes The clot retracted very slightly and was friable During the entire period of observation his platelets were markedly reduced in number Urinalysis: there was a moderate amount of albumin and an occasional coarsely granular cast in the urine There were 4-5 white blood cells per high power field There was no occult blood in the feces

**Clinical Course** During the four weeks following admission to the hospital the patient showed marked improvement, all of the petechiae disappeared, the secondary anemia rapidly diminished, and there was a typical reticulocyte response to fresh liver and iron therapy The stained blood smears at all times showed a great paucity of platelets The bleeding and clotting times were constantly increased, and the clot invariably showed poor retraction and was friable The patient was discharged improved 27 days after his admission to the hospital Three weeks later, while swimming, the patient traumatized the anterior tibial region of the left leg with a resulting large hematoma The patient was followed at intervals in the Out-Patient Department and when last seen 9 months after his admission to the hospital he reported that he had had no evidence of bleeding in the preceding eight months The blood condition remained unchanged throughout this period

*Case 2* M W, unit number 34790, a white, married female, stitcher in a shoe factory, aged 46 years, was admitted to Strong Memorial Hospital complaining of epistaxis, bleeding from the gums, hematomas of the tongue, vaginal bleeding, purpuric spots and many petechiae widely scattered over the entire body For several months she had had a posterior nasal discharge, which had invariably been blood tinged Two weeks prior to admission she had an attack of nausea, vomiting and diarrhea, which lasted 3-4 days Eight days later the posterior nasal discharge contained several blood clots and the gums started to bleed freely On the following day the skin manifestations and the blood-tinged vaginal discharge appeared For four days she had had hematomas along the tongue margins

The family history was irrelevant

**The past history** She stated that she "had always bruised readily". For years her gums had bled readily whenever the teeth were brushed Seven years previously the patient had had cystitis with dysuria and hematuria During the past six years there had been a chronic nasopharyngitis, secondary to a chronic rhinitis, punctuated by acute flareups each winter Over the past five years, hypertension and an obstinate constipation had been present Two years prior to her admission to the hospital she had had an artificial menopause induced by X-ray therapy One year later she had six abscessed teeth removed For four years the patient had been a "stitcher" in a shoe factory, where she came into slight contact with benzol The past history was otherwise negative

Physical examination revealed a well developed and slightly obese female 46 years old, who appeared acutely ill There was no pallor The skin showed numerous small and large petechiae and large purpuric areas The mucous membranes were similarly involved There were small petechiae in the conjunctivae The gums were spongy and bled easily The tongue margins were hemorrhagic The tonsils were enlarged and contained a mucopurulent discharge from the nasopharynx The nares showed a thin watery discharge and the turbinates were slightly enlarged The anterior cervical glands were palpable The heart was slightly enlarged by percussion The aortic second sound was accentuated There was a rough systolic murmur over the aortic area The blood pressure was 200 systolic and 120 diastolic The liver was palpable 1 cm below the costal margin The physical examination was otherwise negative

**Laboratory examinations** The red blood counts ranged between 4,400,000 per cu mm and 5,500,000 per cu mm The hemoglobin values varied from 900 per cent to 1000 per cent The white blood cell counts were consistently between 4,000 per cu mm and 10,150 per cu mm Repeated white blood cell differential counts were entirely normal The reticulocyte count was 20 per cent Examination of a fixed smear on May 1, 1930, revealed complete absence of platelets The red blood cells were normal Following this

the platelets were scarce in repeated fixed stained smears for 50 days, after which time they were fairly abundant. At the time of admission the bleeding time was 90 minutes and the coagulation time (Howell method) was 5 minutes. The blood clot did not retract and was friable. Seventy-one days after admission, the coagulation time (Howell method) was 9 minutes. The blood clot retracted well, was elastic and held its shape when placed on a flat surface. Urinalyses were entirely negative. An electrocardiographic report showed right axis deviation. A blood culture showed no growth in five days.

**Clinical Course** The patient did not bleed profusely at any time while under observation, and all hemorrhage stopped within a few days. The petechiae and purpuric manifestations rapidly cleared. No foci of infection were found. The patient was afebrile while under observation, with the exception of three days when she developed rubella.

**Case 3** J. S., unit number 24698, a white male tailor, aged 28 years, was admitted to the Rochester Municipal Hospital on May 17, 1929, complaining of epistaxis, bleeding from the gums, weakness and dyspnea. The onset was eighteen months before admission to the hospital and was characterized by oozing of blood from the gums. Following this there were intermittent periods of severe epistaxis up to three weeks before admission to the hospital, since which time there had been almost constant bleeding from the nose and gums. Weakness and dyspnea were associated symptoms. There had been no contact with benzol in his work as a tailor.

The family history was irrelevant.

**The past history** He had a bilateral turbinectomy without undue bleeding 4 years before his entry to the hospital. Two and a half years later he had pneumonia and following this an abscessed tooth was extracted. For eighteen months he had had several acute upper respiratory infections. The past history was otherwise irrelevant.

**Physical examination** revealed a well developed and nourished adult Italian male who was very pale. His skin showed many petechiae over the trunk and extremities.

There was a positive Rumpel-Leede phenomenon. The ear drums showed a few petechiae in Shrapnell's membrane. Both nostrils were filled with blood. There were two small areas of ulceration on the left side of the septum and an encrusted area 1 cm in diameter in a similar area on the right side. There were small petechiae on the left wall of the posterior pharynx. The gum margins bled easily upon pressure. The liver edge was barely palpable, and the spleen was not palpable. There were no other abnormal physical signs of any note.

**Laboratory data** On admission the red blood cell count was 2,200,000 per cu mm, the hemoglobin was 40 per cent (Sahl), and the white blood cell count was 2,400 per cu mm. The white blood cell differential count was: neutrophils 49.5 per cent, eosinophils 0.5 per cent, myelocytes 1.0 per cent, metamyelocytes 2.5 per cent, lymphocytes 43.0 per cent, monocytes 3.5 per cent. The total red and white blood cell counts and the hemoglobin remained at essentially the same levels throughout the period of observation. Repeated fixed blood smears stained with Wright's stain revealed a marked reduction in the number of the platelets. The red blood cells showed some achromia and some variations in size and shape. Four days after admission, the bleeding time was 4.5 minutes and the coagulation time was 21 minutes (Howell method). The blood clot did not retract and was friable. The reticulocyte count was 3.5 per cent. Urinalysis and stool examinations were negative. Gastric analysis showed a normal amount of free hydrochloric acid. The basal metabolic rate was -15 per cent. Cultures of the blood were negative. X-ray studies of the chest and teeth revealed no noteworthy abnormal findings. Two salivary counts were 970 and 870 leukocytes per cu mm of saliva.

**Clinical Course** The patient was afebrile throughout the entire period of study. Two days after admission all bleeding from the nose and gums ceased, and the patient was completely free from further bleeding during the next eight weeks. Under fresh liver and iron therapy there was a slight rise in the hemoglobin percentage and the total number of red blood cells rose from 1,900,000 to

2,810,000 per cu mm. This elevation in hemoglobin and in the total number of red blood cells was not maintained. There was a persistent leukopenia, and a constant great reduction in the number of the platelets. The patient was discharged in an improved condition 25 days after admission to the hospital and subsequently was followed in the Out-Patient Department. Ten weeks after admission to the hospital his gums again started to bleed, and two weeks later, several purpuric areas appeared on the legs. Epistaxis began one month following the purpuric areas.

*Case 4* T. M., unit number 31519, a white carpenter, aged 45 years, was admitted to Strong Memorial Hospital Jan. 19, 1930, for relief of epistaxis, bleeding from the gums and purpuric spots. The onset was thirteen days before admission. During this period there had been almost continuous oozing of blood from one or both nostrils, and for five days prior to entry there had been rather general bleeding from the gums. At this time widely scattered purpuric spots first made their appearance. The patient ceased work ten days before admission to the hospital.

The family history was irrelevant.

The past history. At 43 years of age he had had a peritonsillar abscess. Each winter for several years, the patient had had severe "colds" which had been followed by a persistent cough lasting for several weeks.

The marital history was unimportant.

Physical examination revealed a well developed and nourished adult white man, who was anxious but did not appear to be acutely ill. He was pale and there were a few patches of widely scattered petechiae. The buccal mucous membranes and the conjunctivae were pale. There was constant oozing from the gums, the nostrils were encrusted with blood, and the posterior wall of the pharynx was streaked with blood. The spleen and the liver were palpable at the costal margin. The physical examination was otherwise negative.

Laboratory examinations. On admission, the total red blood cell count was 2,480,000 per cu mm, the hemoglobin was 50.0 per cent, and the total white blood cell count

was 800 per cu mm. The differential white blood cell count was: neutrophils 25.0 per cent, eosinophils 1.0 per cent; basophils 1.0 per cent, lymphocytes 44.0 per cent, and monocytes 20.0 per cent. The red blood cells showed no achromia. There was distinct anisocytosis. Numerous basophilic red blood cells were present. No platelets were found. The coagulation time was 9 minutes (Howell method) and retraction of the clot was poor. The icterus index was 6. The blood platelets remained much reduced in numbers during a period of 6 months. Five months after the patient was first seen the coagulation time was 4 minutes. The blood clot retracted poorly and was friable. The bleeding time was 12 minutes. The red blood cell count at this time was 5,200,000 per cu mm and the hemoglobin was 98.0 per cent, (Sahli). Following this there was a moderate drop in both the red blood cell count and the hemoglobin. The white blood cell count remained low throughout the period of observation, the highest count being 2,600 per cu mm. 5 months after his first admission to the hospital. The average value was approximately 2,000 per cu mm with, at all times, a diminished percentage of neutrophils. Urinalyses were entirely negative throughout his period of observation. On four occasions there were positive guaiac tests for occult blood in the feces. A salivary count on Jan. 20, 1930, was 180 cells per cu mm. Six months later it was 260 cells per cu mm.

Clinical Course. Direct blood transfusions readily controlled the bleeding. The purpuric spots rapidly disappeared. After two weeks of complete freedom from bleeding, the patient again had a five day period of oozing of blood from the nostrils and gums. The only other evidence of bleeding while the patient was in the hospital was the presence of occult blood in his stools, occurring three weeks later. One month after admission to the hospital a third direct blood transfusion was given. From this time the patient made rapid subjective improvement. During his stay in the hospital the patient was afebrile after the fourth day. He received intensive liver therapy, cod-liver oil, and ultraviolet radiations. He was discharged improved 38 days after his admission. For the next two months he made steady progress. At rare

intervals he had slight bleeding lasting for several hours, and, occasionally, he noted a few scattered purpuric spots on his body. The patient resumed part time work at carpentering. However, on April 30, 1930, about three months after his discharge from the hospital, oozing of blood from the nostrils and the gums again started, and continued more or less constantly up to his readmission 5 weeks later. The physical examination at this time was essentially that of the first admission with the exception that the spleen was not palpable, and that there was a positive Rumpel-Leede phenomenon. Five days after his second admission to the hospital the patient bled profusely following biopsy of a gland in the left axilla. A direct blood transfusion of 300 cc was required to control this. The patient again made rapid improvement. He was discharged improved 27 days after his second entry. Three weeks after his discharge from the hospital he reported that he had had almost constant oozing of blood from the gums since he left the hospital. Occasionally he had noticed a few petechiae on his arms and legs. When seen 3 weeks later he had had no further bleeding and was in good general condition.

**Case 5** J G, unit number 27308, a white messenger boy, aged 17 years, was admitted to the Rochester Municipal Hospital on August 22, 1929, on account of a fistula in ano, tiredness, dyspnea, weakness, and epistaxis. For six months he had tired easily. One month prior to his admission to the hospital he developed an ischiorectal abscess. Subsequently there was an associated fistula in ano which drained continuously up to his entry to the hospital. Epistaxis which recurred at weekly intervals, with varying intensity, had been present for one month. For two weeks the gums had showed slight oozing of blood. For several months he had noticed that he bruised easily. Tiredness, dyspnea, and weakness had been progressively more pronounced during the month preceding his admission to the hospital.

The family and past histories were irrelevant.

**Physical examination** The patient was a well developed and nourished white boy of

seventeen years who appeared acutely ill. There was marked pallor. Petechiae were present over the anterior chest and about the pelvis. There was one purpuric spot on the shaft of the penis. The mucous membranes were very pale. There was a large purpuric spot on the soft palate and several on the posterior pharyngeal wall. There was some fresh blood on the upper pole of the left tonsil, and on the gums. The nasal septum showed slight oozing of blood. Slight general glandular enlargement was present. There was a discharging left fistula in ano. No other relevant abnormal physical signs were present.

**Laboratory examinations** Six days after admission to the hospital the red blood cell count was 2,400,000 per cu mm, the hemoglobin was 40.0 per cent, and the total white blood cell count was 3,800 per cu mm. The differential formula for the white blood cells was: neutrophils 27.0 per cent, eosinophils 1.0 per cent, lymphocytes 69.0 per cent, and monocytes 3.0 per cent. The reticulocyte count was 0.4 per cent. The blood Wassermann was negative. A blood culture was sterile. The icterus index was 4. The bleeding time was 6 minutes and the coagulation time was 21 minutes. The clot did not retract in 12 hours and was friable. In a fixed smear, the red blood cells showed some achromia and slight variations in size and shape. No platelets were found. For a period of approximately 3 months the red blood cell count and the hemoglobin values were kept between 800,000 per cu mm and 17.0 per cent, respectively, and 2,650,000 per cu mm and 50.0 per cent by repeated transfusions. The total white blood cell count, the differential formula and the percentage of reticulocytes remained remarkably constant during this time. Following this, there was a fairly good reticulocyte response (6.0 per cent), after which the red blood cell count, the hemoglobin, the white blood cell count and the percentage of neutrophils increased. Seven months after the patient's entry to the hospital his total red blood cell count was 3,740,000 per cu mm, his hemoglobin was 84.0 per cent, and his total white blood cell count was 4,400 per cu mm. At this time the coagulation time was 17 minutes and there was only slight retraction of the clot.

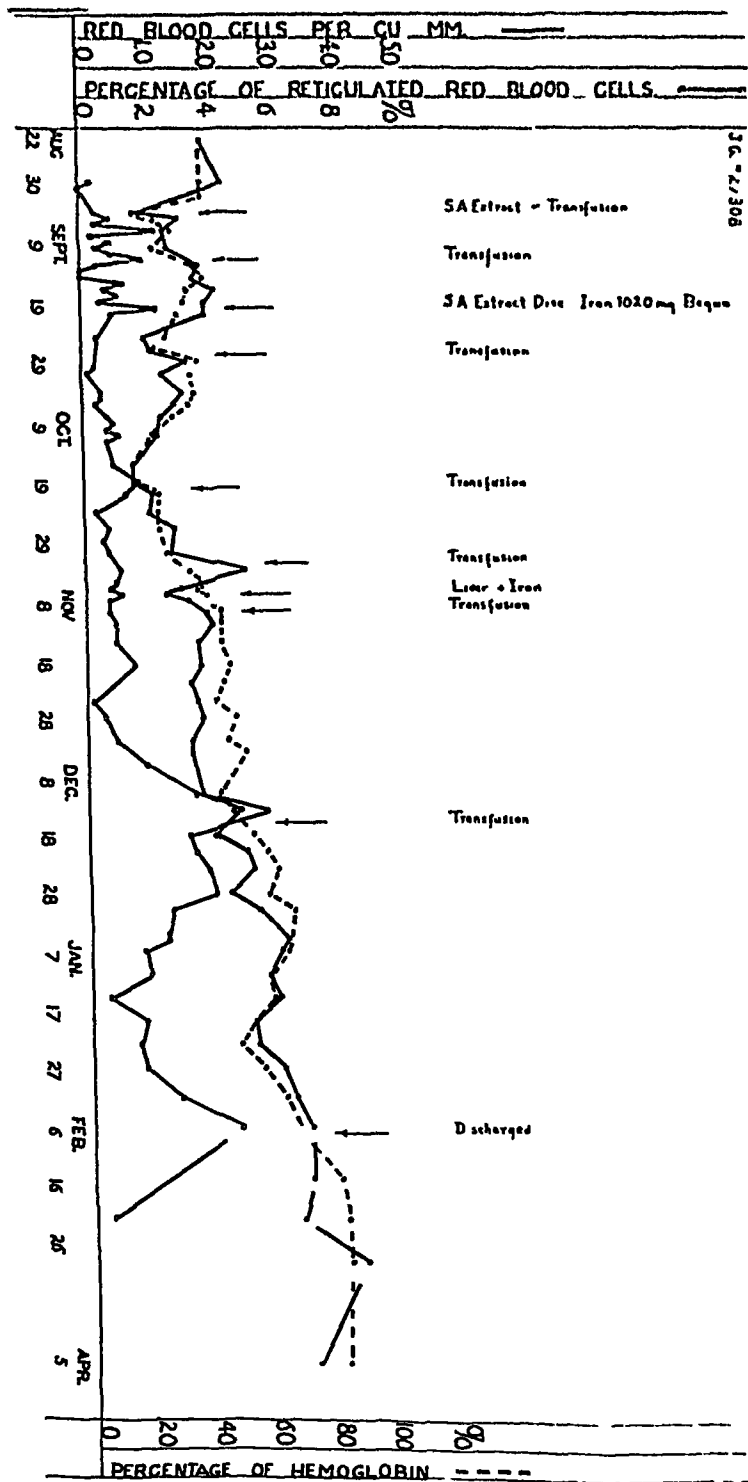


CHART I The red blood cell count and the percentage of hemoglobin and reticulated red blood cells at various times in the blood of Case 5, J G, unit number 27308

Chart I shows the principal changes in this patient's blood during his period of observation. Urinalyses were negative throughout his stay in the hospital. There was a normal amount of free hydrochloric acid in the gastric contents. X-ray examinations of the chest, the sinuses and the teeth were negative.

**Clinical course** The only demonstrable focus of infection was the fistula in ano, which responded rapidly to treatment. During the eight weeks following admission, the patient received four transfusions of citrated blood, of about 500 cc each. On the second week, Secondary Anemia Extract<sup>7</sup> was started. On the fourth week this was discontinued, and large daily doses of iron were substituted. Under this régime there was a steady fall in the blood cell counts, from 2,850,000 to 800,000 per cu mm, with a corresponding drop in hemoglobin percentage from 40 to 15 per cent. There was a constant leucopenia, averaging 2,000 white blood corpuscles per cu mm. Stained blood smears showed a marked paucity of platelets at all times. The reticulocytes varied from 0.4 per cent to 2.5 per cent. The clotting time (Howell method) was prolonged. The clot failed to retract in twelve hours and was friable. During this period the patient had intermittent bleeding from the nose and gums, also several retinal hemorrhages. On the eleventh week after admission, whole liver (100 gms daily) was started, the iron being continued as before. Over the next five weeks, four more transfusions, each of about 500 cc of citrated blood, were given. About a month following this change in therapy, the hemoglobin percentage rose from 47 per cent, on Dec 1, to 85 per cent on Feb 21, and the red blood cell count increased from 1,380,000 to 3,510,000 per cu mm, while the white blood cell count rose to an average of 5,000 per cu mm. The platelets, at all times, were greatly reduced in numbers. The clotting time was prolonged, the clot failed to retract in 12 hours, and was friable. On the sixteenth and twenty-fifth weeks there were reticulocytic responses of 6.0 per cent and 5.0 per cent respectively. All active bleeding stopped, although purpuric manifestations on bruising, and a positive Rumpel-Leede phenomenon still per-

sisted. The patient was discharged on Feb 21, greatly improved. On March 6, 1930, circumcision was performed without undue bleeding. On April 5, 1930, the hemoglobin and the red blood cell count were essentially the same as in February, the platelets were still greatly reduced in numbers and the clotting time (Howell method) was 17 minutes. The clot failed to retract after 12 hours, and was friable. There had been no further bleeding.

## DISCUSSION

These five cases have one thing in common, namely, a marked reduction in the number of the platelets in the peripheral blood in the absence of any known etiological agent. No data are available that will allow any positive assertion as to the exact mechanism which is responsible for the scarcity of the platelets in the peripheral blood. As long as there remains any legitimate skepticism as to the source of the blood platelets and no satisfactory test that may be used to determine whether these elements are being destroyed in the peripheral blood, just so long must there be an inability to explain positively the mechanism which is responsible for diminished, or absent platelets in the blood of any given patient. However, correlation of various data may give strong presumptive evidence of the process at fault in some instances. For example, the presence of large amounts of invading tissue in the bone marrow in the leukemias, metastatic malignancies, and similar conditions are generally conceded to be the explanation for the diminution in platelets in the blood stream when this occurs in such conditions. Again, aplasia of the bone marrow such as is found in aplastic anemia is taken as the explanation for the reduction in the number of the platelets

in this disease. A specialized type of purpura associated with marked aplasia of the bone marrow in dogs treated with roentgen irradiation over all of the bones has recently been reported by Shouse, Warren and Whipple<sup>6</sup>. The fact that the megakaryocytes in the bone marrow of such dogs, have disappeared is particularly pertinent. In idiopathic types of purpura such as are reported in this paper, the evidence of bone marrow disorder may be less clear. Particularly is this true, when the platelets are the only one of the three formed elements of the blood that are involved, as is true in cases 1 and 2. Since no positive answer can be given in such cases, we shall not attempt to give any explanation of the process involved. We realize that any one of the following possibilities may be at fault in these cases. First, the platelets may be reduced as a result of diminished numbers manufactured by the bone marrow. We agree with Wright<sup>8</sup> that the megakaryocytes of the bone marrow are the most likely elements involved in such a process but realize that this hypothesis is not absolutely proven. Second, there may be increased destruction of the platelets in the peripheral blood. This includes the possibility suggested by Kaznelson<sup>3</sup> that the spleen may be actively involved in such cases. Third, there may be an increased migration of the platelets through the vascular walls. No evidence that we know of has ever been presented to indicate that such a condition exists. Fourth, there may be a combination of any of the above possibilities. Cases 1 and 2 can be explained equally well by any of these four theoretical possibilities.

Cases 3 and 4 show, in addition to a marked reduction in the number of the platelets in the blood, a diminution in the total number of the white blood cells and, in particular, a reduction in the number of circulating granulocytes. Reduction in the number of the granulocytes is frequently taken as evidence of bone marrow insufficiency as regards the white blood cell element. However, this is not a necessary explanation of such a condition. Increased destruction of these cells in the peripheral blood or increased elimination of such cells from the vascular system will satisfactorily explain such a picture. Unfortunately there is no reliable test for increased peripheral destruction of the granulocytes. Further, there is only one test that is at all satisfactory for indicating increased elimination of granulocytes from the peripheral blood. This is the salivary count as given by Isaacs and Danielson<sup>2</sup>. The elevation of the salivary count to twice the upper limit of normal in Case 3 indicates that this process *may* have been responsible, at least in part, for the leucopenia in this patient. Such evidence was not present in Case 4, which had a tremendous reduction in the total number of all the white blood cells and, in particular of the granulocytes. The picture present in this patient could be explained perfectly by the assumption that the white blood cell and the platelet functions of the bone marrow were reduced. No positive evidence for this assumption can be given, but on the other hand, no data are forthcoming that are inconsistent with such a state of affairs.

Case 5 had a tremendous reduction in the number of platelets in the peri-

pheral blood, considerable reduction in the total number of white blood cells and in the granulocytes, and absence of all signs of regeneration of hemoglobin and red blood cells. In other words, all of the formed elements of the blood were reduced in numbers. Unfortunately, no salivary counts were obtained in this patient. The stained smear of the blood showed no evidence of fragmentation of the red blood cells and the icterus index was low. Hence, the evidence for increased destruction of the red blood cells in the peripheral blood was lacking. No evidence either for or against increased migration of these cells from the peripheral blood is present. On the other hand, the almost complete absence of reticulocytes and polychromatophilic cells is strong presumptive evidence that the bone marrow was deficient as regards the formation of red blood cells. The simplest explanation for the whole blood picture in this case would be logically that all of the functions of the bone marrow as regards the three formed elements, were reduced or completely inhibited for a period of time. The later assumption of approximately normal values for hemoglobin, red blood cell and white blood cell counts in this patient suggests that these functions of the bone marrow recurred. The continued diminution in the numbers of the platelets may be due to any one of the four theoretical possibilities mentioned previously. It does seem however that in as much as there was a very good possibility of the bone marrow being involved in this case explanation for the platelet de-

ficiency may be found in bone marrow insufficiency.

Cases 3, 4 and 5 represent what have been termed intermediate types of purpura hemorrhagica<sup>147</sup>. That is they show the blood pictures which one might assume, on theoretical grounds, would be shown by patients who had conditions intermediate between true purpura hemorrhagica, as illustrated by Cases 1 and 2, and aplastic anemia. Case 5 simulates this latter condition very closely. Since the two conditions may simulate one another so closely, it may be well to emphasize this fact with reference to the difficulty in differentiating atypical forms of these conditions. A positive diagnosis of true aplastic anemia is, at best, a difficult task and is open to question as long as the patient remains alive. It would seem advisable to consider the diagnosis of aplastic anemia as questionable until a thorough trial of blood transfusions and of therapeutic measures for anemia has been given the patient. It seems highly unlikely that Case 5 would have survived had not such a procedure been adopted.

#### CONCLUSIONS

1. Five patients with different types of idiopathic thrombopenic purpura have been reported.

2. Various theoretical mechanisms which may be present in idiopathic thrombopenic purpura have been mentioned.

3. The close similarity between aplastic anemia and certain atypical forms of idiopathic thrombopenic purpura has been stressed.



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# Chronic Mercurial Poisoning Simulating Acute Cholecystitis and Choledocholithiasis\*

(Report of a Case)

By J WILLIAM HINTON, M D , F A C S , *Assistant Professor of Surgery, New York Post-Graduate Medical School and Hospital Assistant Attending Surgeon, Bellevue Hospital, New York City*

ATTENTION has been called during the past few years to the fact that heavy metals often cause acute toxic hepatitis which may produce symptoms quite similar to infection and calculi of the biliary tract. Arsenic, lead and mercury are the metals most frequently found in the hepatic changes and Vogel<sup>2</sup> has stressed the importance of examining the urine of all jaundiced patients for arsenic. In his paper it is interesting to find that in 40 jaundiced patients 34, or 85 per cent, contained arsenic in the urine, and in 9 out of 34 cases in which arsenic and jaundice occurred simultaneously death resulted. In 4 of these cases death promptly followed an operation on the biliary tract.

Myers and Throne<sup>3</sup> emphasized the possibility of heavy metals entering one's system through occupational sources and from water and food supplies. Lead drinking pipes are a frequent source of contaminated water, according to them, and green vegetables and raw fruits sprayed with dif-

ferent insecticides are another. It would seem that, in the past, patients with jaundice have been operated upon for cholecystitis and cholelithiasis without finding sufficient pathology to account for the symptoms and unquestionably some of these patients succumbed from an unrecognized metal poisoning with acute toxic hepatitis.

*Case report* Male, age 33, admitted to the Fourth Surgical Division, Bellevue Hospital, June 2, 1930. *Chief complaint* Jaundice and pain in epigastrium. *Past history* Negative with the exception of an attack of influenza 5 years ago. *Present illness* Six months before admission patient's attention was called to the yellow color of his skin. A short while after this he began having dull pain in the epigastrium and later the pain became more severe and he had attacks of pain in epigastrium and right upper quadrant at which time it was thought he became more deeply jaundiced. The pain was never excruciating in character, although he was never free from abdominal discomfort. At times the pain would radiate to the right lumbar region. When the jaundice was deepest the patient had clay colored stools, though they appeared normal between attacks. He lost 20 pounds in weight 8 or them in the past 2 weeks and he had been unable to work for the past 6 weeks.

\*I wish to thank Dr Carl G Burdick, Director of the Fourth Surgical Division, Bellevue Hospital, for the privilege of reporting this case.

*Examination* Patient was deeply jaundiced, including skin, sclera and mucous membrane. Heart normal and blood pressure 103 over

60 Abdomen slight rigidity in right upper quadrant and some tenderness on deep palpation in epigastrium, but no definite gall bladder tenderness. Liver was enlarged 3 fingers below the costal margin and there was a moderate amount of fluid in abdomen. Spleen could not be palpated. Temperature 104 on admission with 21,400 leukocytes and 86% polys. Urine albumin 3 plus, bile 4 plus. Microscopic examination negative. Admission diagnosis of house staff, Acute exacerbation of chronic cholecystitis and choledocholithiasis. Admission note presented by the patient from the Vanderbilt Clinic dated June 2, 1930 temperature 104.8 with 26,000 leukocytes and 94% polys.

*Diagnosis* Acute cholecystitis. Patient was referred to Bellevue Hospital as there were no vacancies available in the other institution. After reviewing the history it was thought the patient might possibly have a chronic metal poisoning causing an acute toxic hepatitis as he had been employed for

the past several years by a carpet manufacturing company to inspect finished rugs. Laboratory work June 3, 1930, revealed sugar 80, creatinine 1.3, chlorides 525, calcium 12, phosphorus 2.5, cholesterol 272, N P N 23, urea nitrogen 14. Bleeding time 7 minutes, 50 seconds and clotting time 7 minutes, 45 seconds. Icterus index 33.3, Vandenberg indirect 3, direct 2, Fouchet 3. June 5, 1930, 24 hour specimen of urine done in Dr. Gettler's laboratory revealed a fair amount of mercury present, arsenic absent. June 9, 1930, dye test does not visualize gall bladder.

*Treatment* On June 3, 1930, patient was given calcium chloride 20 c c of 10% solution, intravenously, and the same was repeated on the 4th, 5th, 6th and 7th. Glucose 50 c c of 20% solution was given intravenously on the 8th, 9th, 10th, 11th, 12th, 13th, 14th, 15th, 16th and 17th. Sodium thio-sulphate 15 grains given on the 10th, 11th and 12th. Patient ran a septic temperature for the first 5 days, temperature ranging

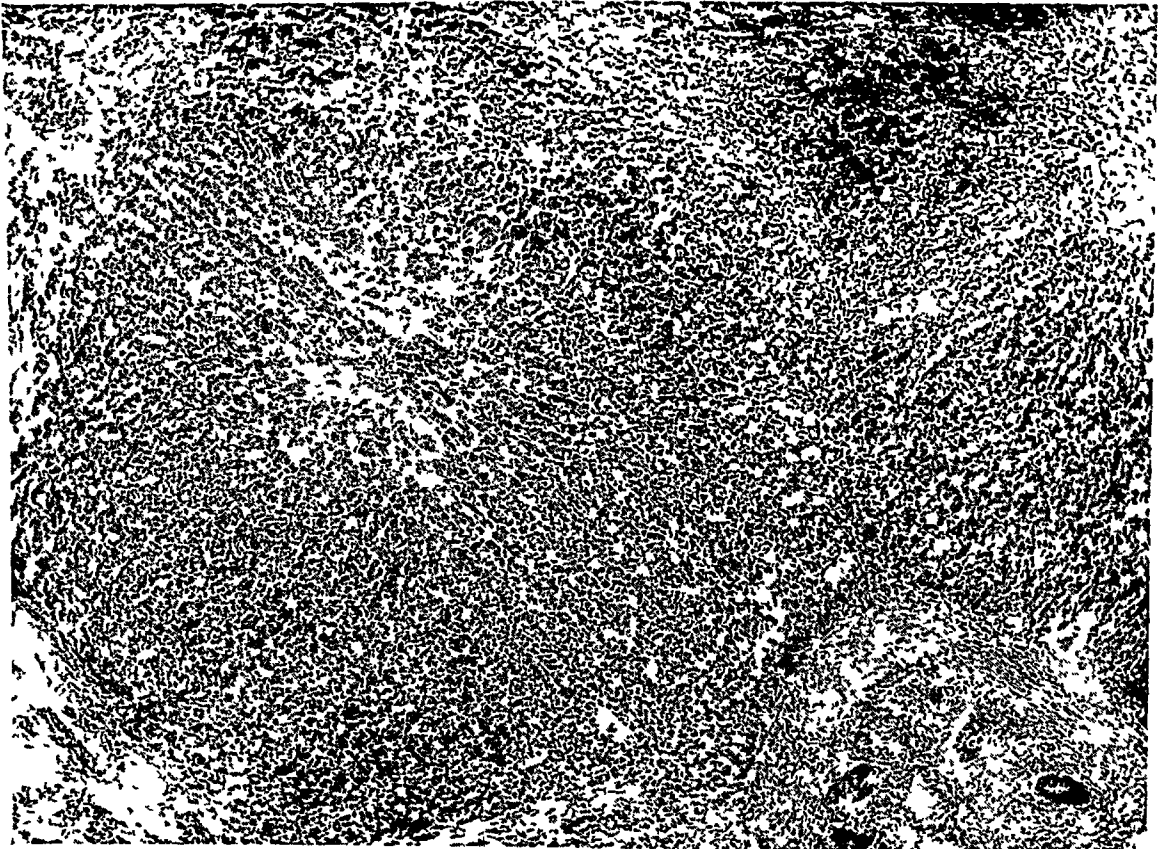


FIG 1 Shows central necrosis with acute toxic hepatitis and chronic interstitial hepatitis at the periphery

from 100 to 104.5. On the 6th day his temperature became normal and it was noticed at that time that the jaundice was definitely subsiding and his abdomen was not tender, nor was there any fluid present. Urine examination June 19, 1930 negative for mercury and his jaundice had improved about 75 per cent with a slight reduction in the size of the liver. Patient was given dilute hydrochloric acid 10 T I D. Urine analysis on June 27, 1930 revealed a trace of mercury present. The acid was continued and the urine was positive for mercury on July 5th. He was symptom free with the exception of the slight jaundice and the enlargement of the liver. Patient again placed on calcium chloride intravenously July 6th 20 c c of 10% solution and this was continued daily until July 19th. Urine was still positive for mercury and the patient was then placed back on dilute hydrochloric acid 20 mm Q 4 H. His jaundice was still present but on July 17th he began running a slight septic tem-

perature. This continued and on the 21st his jaundice had slightly deepened and he had a temperature ranging from 99 to 102. Urine positive for mercury on July 22nd but negative on July 29th. It was decided on July 29th that an exploratory operation was indicated as the patient was continuing to run the septic temperature and his jaundice was deeper than two weeks previously but 50 per cent better than on admission. His urine was negative at this time and it was thought that a cholecystitis and choledocholithiasis might possibly be associated with the mercury poisoning. Operation August 1st. On opening the abdomen the liver was found markedly enlarged and extending 3 fingers below the costal cartilages. No nodules or irregularities detected, but it was of a reddish gray color. The gall bladder was found thickened and grossly diseased but no stones palpated in the gall bladder or common duct. Stomach and duodenum negative to palpation. Pancreas did not feel thickened or en-

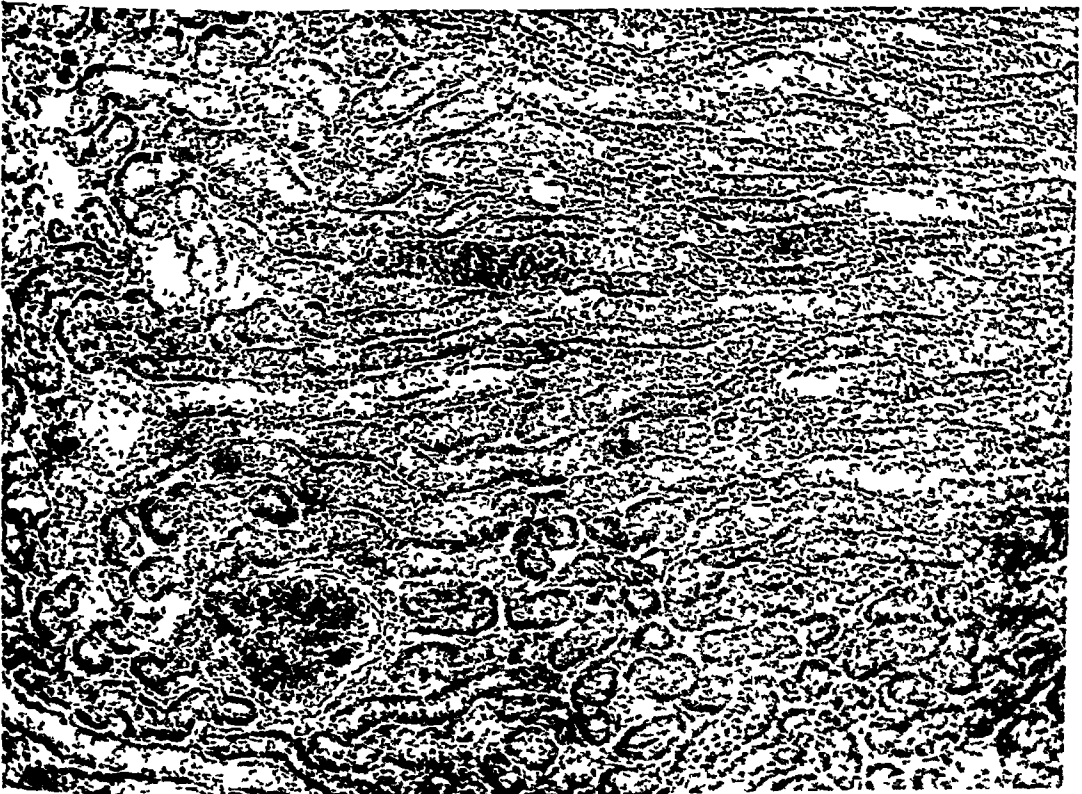


FIG 2 Extensive degeneration and necrosis of tubular epithelium

larged but numerous lymph glands were felt along the common and cystic ducts. Cholecystectomy done and sections taken from both right and left lobes of liver for histologic study. The liver was extremely friable and very difficult to suture and the suture cut through even when taken in mattress form. By macroscopic appearance the liver was definitely diseased. Abdo-

men closed in anatomical layers with a cigarette diam.

*Post-operative* The patient reacted fairly well for 48 hours but then gradually declined in spite of intravenous glucose, hypodermoclysis and other supportive measures, and his death was typical of a cholemia.

*Autopsy* The liver is markedly increased in size weighing 2300 gms. The capsule is



FIG 3 Tumor seen arising around ampulla of Vater  
"A" Probe in common duct  
"B" Probe in duct of Wirsung

unchanged On section the liver substance is very soft in consistency and very friable The color is a dark greenish, slate-gray The natural lobular markings of the liver are entirely obliterated and replaced by a soft homogeneous mottling The consistency of the liver substance is so friable as to tear easily under manipulation There is very little fibrous tissue replacement No metastatic nodules can be found The microscopic appearance is illustrated in Figure 1 A trace of mercury was found on chemical analysis of the liver The kidneys are slightly increased in size and are noticeably edematous On section the cortex and medulla are fairly well differentiated The cortex is increased in size and edematous pale in color with a slight violet tint and the natural markings are hazy and obscured The pyramids are more definitely of a violaceous tint than the cortex The markings of the pyramids are not definitely altered The capsule strips off with increased difficulty and leaves be-

hind it a smooth, glistening, pale, homogeneous surface The amount of fat in the pelvis is slightly increased Figure 2 reveals tubular degeneration and necrosis A trace of mercury was found on chemical analysis of the kidneys Duodenum The ampulla of Vater is markedly increased in size and appears as an irregular nodular fungating tumor mass about 5 to 6 cm in diameter The outer border of this mass is definitely raised, whitish in color and definitely harder in consistency than the surrounding intestine In the center of the mass is a deep eroded depression about  $1\frac{1}{2}$  cm in diameter, representing the opening of the common and pancreatic ducts This area is of a dirty grayish color, necrotic and very friable in consistency The base of the tumor mass extends to the outer wall of the duodenum Figure 3 illustrates the tumor at the ampulla of Vater In Figure 4, it is seen to be an adeno-carcinoma The pancreas is apparently natural throughout its entire substance,

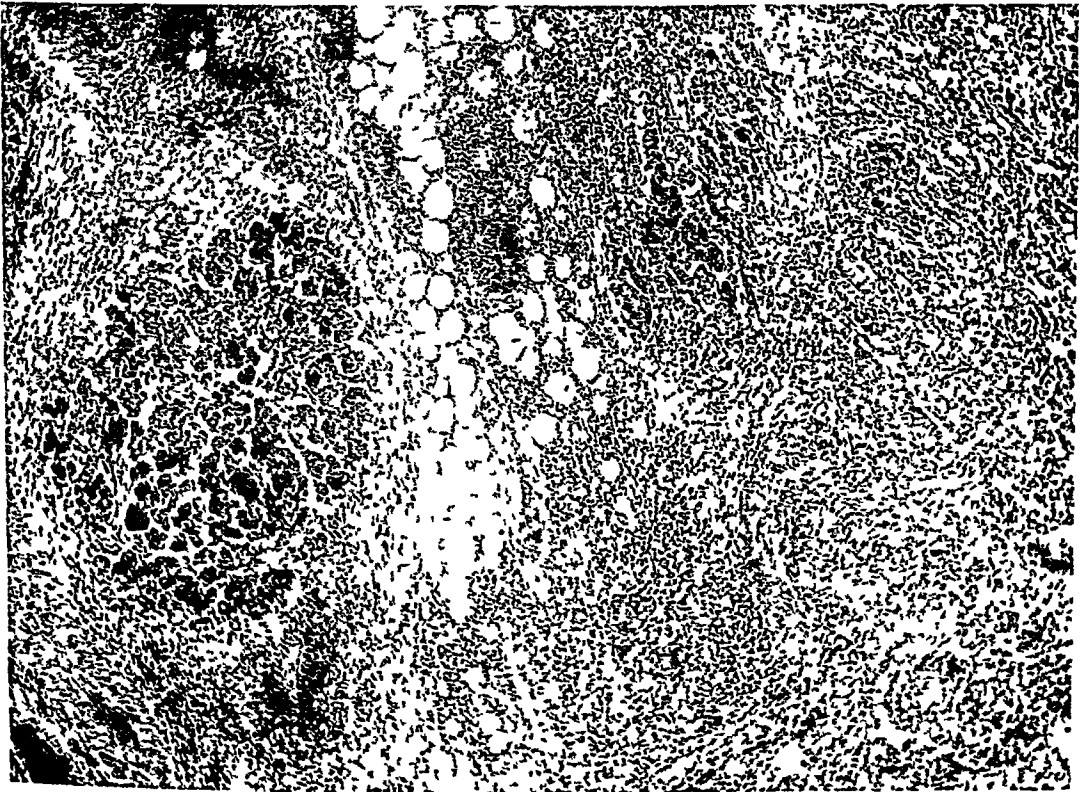


FIG 4 Histologic section reveals the tumor, adeno-carcinoma

showing no areas of infiltration or induration. However, it is adherent to the under side of the duodenum directly under the tumor mass and apparently attached to it. Probes can be passed through the common duct and pancreatic duct, but with difficulty. The primary cause of death was due to the mercurial poisoning with destructive liver and kidney changes. The duodenal tumor was an incidental finding.

#### COMMENT

This patient gave a history which could be interpreted as typical of a stone in the common duct with an associated cholecystitis and if measures had not been taken to rule out metal poisoning he would have been operated upon immediately. The improvement in this patient when put on calcium chloride and glucose, intravenously, was most startling. His temperature became normal in a few days, jaundice started to improve immediately after treatment was begun, and mercury was absent in urine in 16 days. Then,

after placing the patient on dilute hydrochloric acid, mercury was again present in the urine, and the urine remained positive for the next 6 weeks, although he was placed back on calcium chloride intravenously from July 6th to the 19th. The urine became negative again July 29th but the patient at that time was running a septic temperature and was more deeply jaundiced.

A recent editorial<sup>1</sup> in the Journal of the American Medical Association called attention to the treatment of chronic mercurial poisoning by the administration of alkalis in the acute stages of intoxication, thus inhibiting the elimination of the metal from the liver and bone marrow while the symptoms of acute poisoning existed. After the acute stages of intoxication have subsided acids can be given to complete the elimination of the metal from the body which has been inhibited by the administration of alkalis.

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# The Diagnosis of Pre-Clinical Tubercle in Suspects and Contacts by Caulfeild's Inhibitive and the T.C.F. Clinical Application:

## Part II. Graphs and X-Rays\*

By WILLIAM E. OGDEN, M.D., (Tor.), *Director, D.P.H. Chest Clinic, Toronto Western Hospital, Consultant in Diseases of the Chest, Department of Pensions and National Health, Toronto, Canada*

IN the "Annals" of October, 1930, Part I<sup>11</sup> of this paper gave ten points for guidance in the use of serology for diagnosis in tuberculosis, together with certain limitations. I included histories of ten examples of Tb suspects in which, at first examination no positive diagnosis could be made by any of the usual methods of clinical history, p.s. (physical signs), examination of sputum or stereo-X ray films (where obtainable). In each of these, examination of the blood serum indicated the diagnosis for or against tubercle, which diagnosis was later proved correct by positive sputum or X-ray stereograms, etc. None of the X-ray pictures and serological graphs shown on the screen at Minneapolis<sup>#</sup> were published in Part I.

I shall now give graphs or X-rays of

three Tb suspects whose complete histories were detailed in Part I. Their stories will be understood here, without the histories. After that I shall proceed to give ten examples of Tb contacts complete with histories, serology and X-rays with lessons to be learned therefrom.

### THE USE OF GRAPHS IN THE STUDY OF SERIAL SEROLOGICAL REACTIONS

Since Caulfeild introduced graphs for this purpose, five years ago, we have found the significance of serial tests more easily demonstrated by this method.

The month and year of each test is noted at the top of vertical columns (see specimen below). Fifteen or twenty columns allow for the recording of the same number of tests which are not done oftener than once a month, unless to check possible laboratory error. Fixations are noted by crosses and connecting lines in black; inhibitives by circles and connecting lines in red.

The degree of reaction is represented by horizontal lines. Fixation is record-

\*These lantern slides were shown before the Academies of Medicine in Toronto and Cleveland, 1929. Final paper before the American College of Physicians, Minneapolis, Minn., February, 1930.

<sup>#</sup>Illness prevented me transferring these to paper for the October issue. They were given at the meeting from lantern slides and memory.



ed in half units, from a negative base line, which is the normal, to two units which is positive, and three units, very strong positive. The inhibitive is recorded in classes starting from a negative base line which is the normal in infants, then a very slight inhibitive, normal in the adult, up to second class which is positive, and first class, very strong positive. The latter reaction, viz, first class inhibitive is not common.

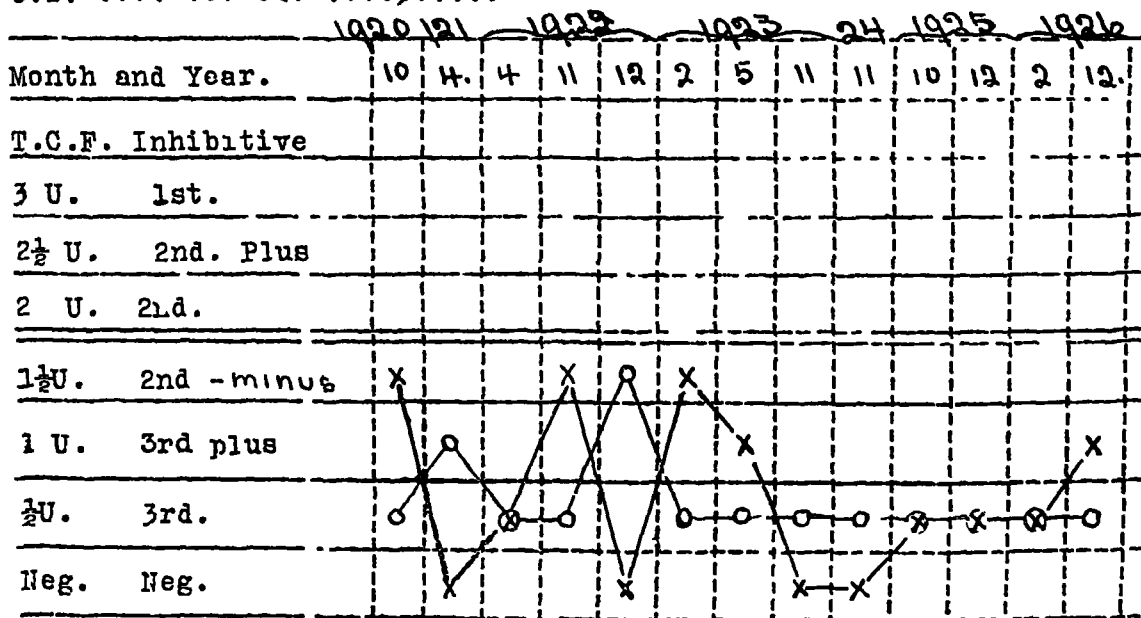
The terms "first and second class" originated in their prognostic significance. Tuberculous patients giving repeated second class inhibitives are as a rule doing well, at least are reacting well biologically, and inferentially, more likely to do well clinically. Those giving "first class" inhibitives do better

still (have a "first class" outlook), instance case No. 3 (M<sub>1</sub> P), Part I, p 383. His two positive inhibitives were first class; although commencing with tubercle bacilli in the sputum, July, 1919, he made his cure with only moderately restricted routine, his steroids in 1920 and April, 1921, failing to show even a demonstrable lesion. But, the subject at the moment is diagnosis, the digression is to explain terminology, prognosis has been dealt with elsewhere by Caulfield<sup>2,7</sup> and once by myself<sup>3</sup>.

With these serological aids to diagnosis in our ex-soldier chest cases, since the inception of the clinic in 1918, we feel we have had unique facilities. Instance TB suspect examples Nos 2

#### EXAMPLES OF TUBERCULOSIS SUSPECTS DIAGNOSED BY SEROLOGY

NAME *Example of Tb. suspect. Reg. No. 193423.*  
O.D. *CASE 8 (Flah).....*



Serial serological graph of suspect

CASE 8 (Flah) was a Tb suspect 7 years. Note 13 double tests within normal limits, then satisfactory diagnosis other than tubercle was made, viz bronchiectasis (Part I, p 384). This will serve also as a normal graph.

and 3 detailed in Part I, and Nos 8 and 9 given above. In these four cases, however, the collaboration of the serodiagnosis was unusually delayed. These four were Department patients. No 2 was an army nursing sister, later referred by Dr Gordon Gallie, as private patient.

EXAMPLES OF TB CONTACTS WITH  
PRECLINICAL OR POTENTIAL TUBER-  
CULOSIS DIAGNOSED BY SEROLOGY,  
AND SUBSEQUENTLY DEVELOP-  
ING CLINICAL TUBERCULOSIS

I shall give ten examples of the TB contact class in which serology was of the greatest value. In half of these one might reasonably have expected the disease to have become irreparably advanced had not positive serological tests told us to hold on to the cases.

It will be noted that none were followed because of symptoms.

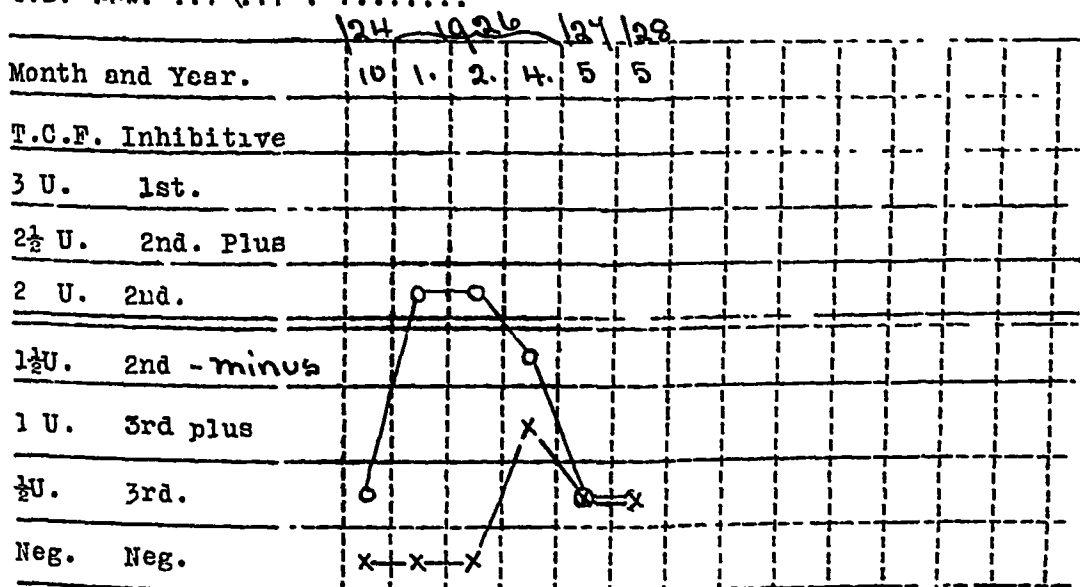
The public is not yet "contact-conscious" (Caulfeild<sup>12</sup>). Four only, of my ten examples to be given, were "contact-conscious" and came on their own initiative. Three others were seized upon by the writer rather against their wish, and the remaining three were sought out as contacts by the Toronto D P H follow-up system.

In my ten examples I have deliberately chosen seven who subsequently developed clinical tuberculosis; they are of greater interest. The actual proportion of all adult contacts developing lesions may be less than the inverse of this percentage.

Of these seven developing lesions all did so while *under my observation*, five

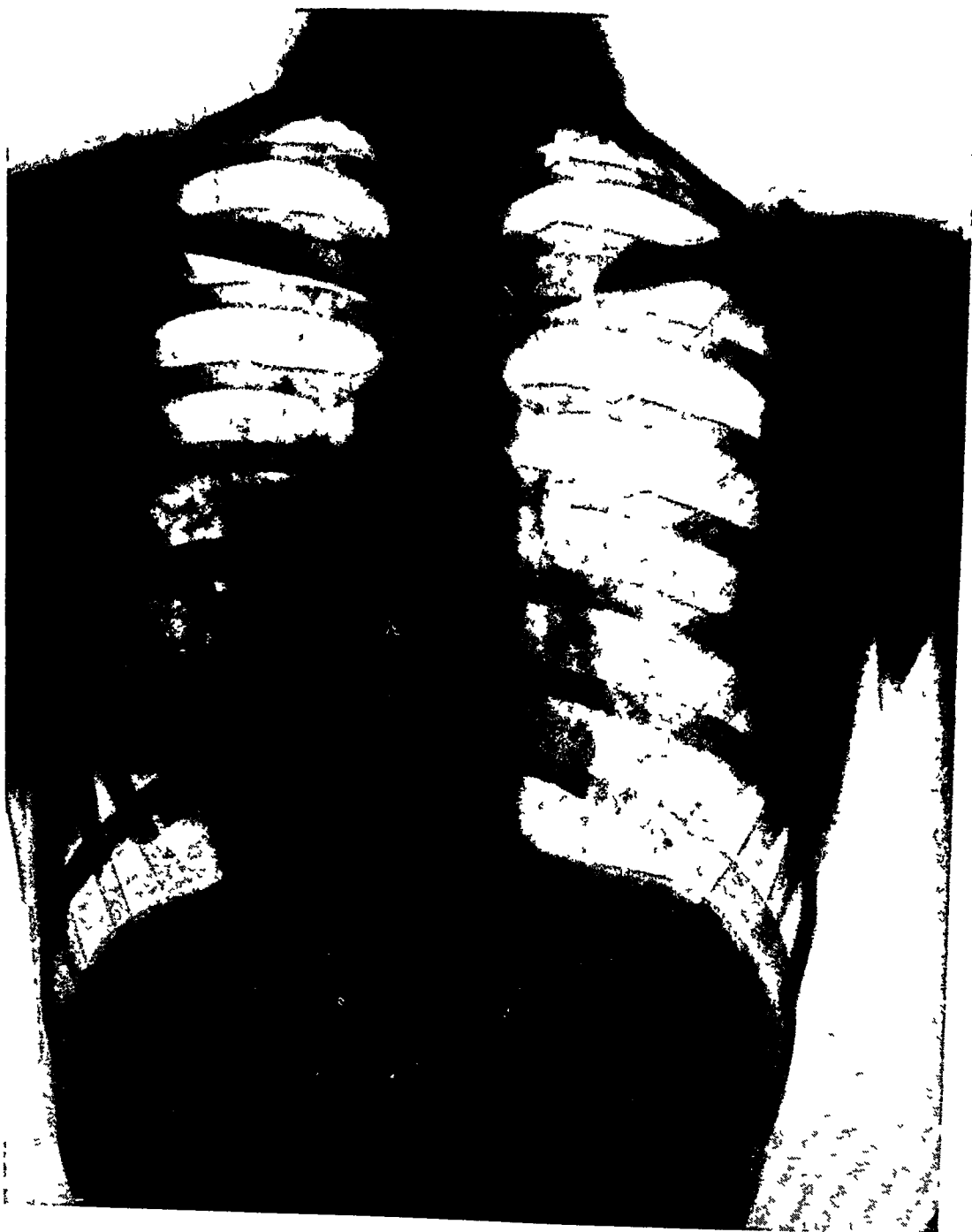
NAME *Example of Tb. suspect* .....

O.D. *Case 9 (R.M.) (W.S.C. 162252)*



Serial serological graph of suspect

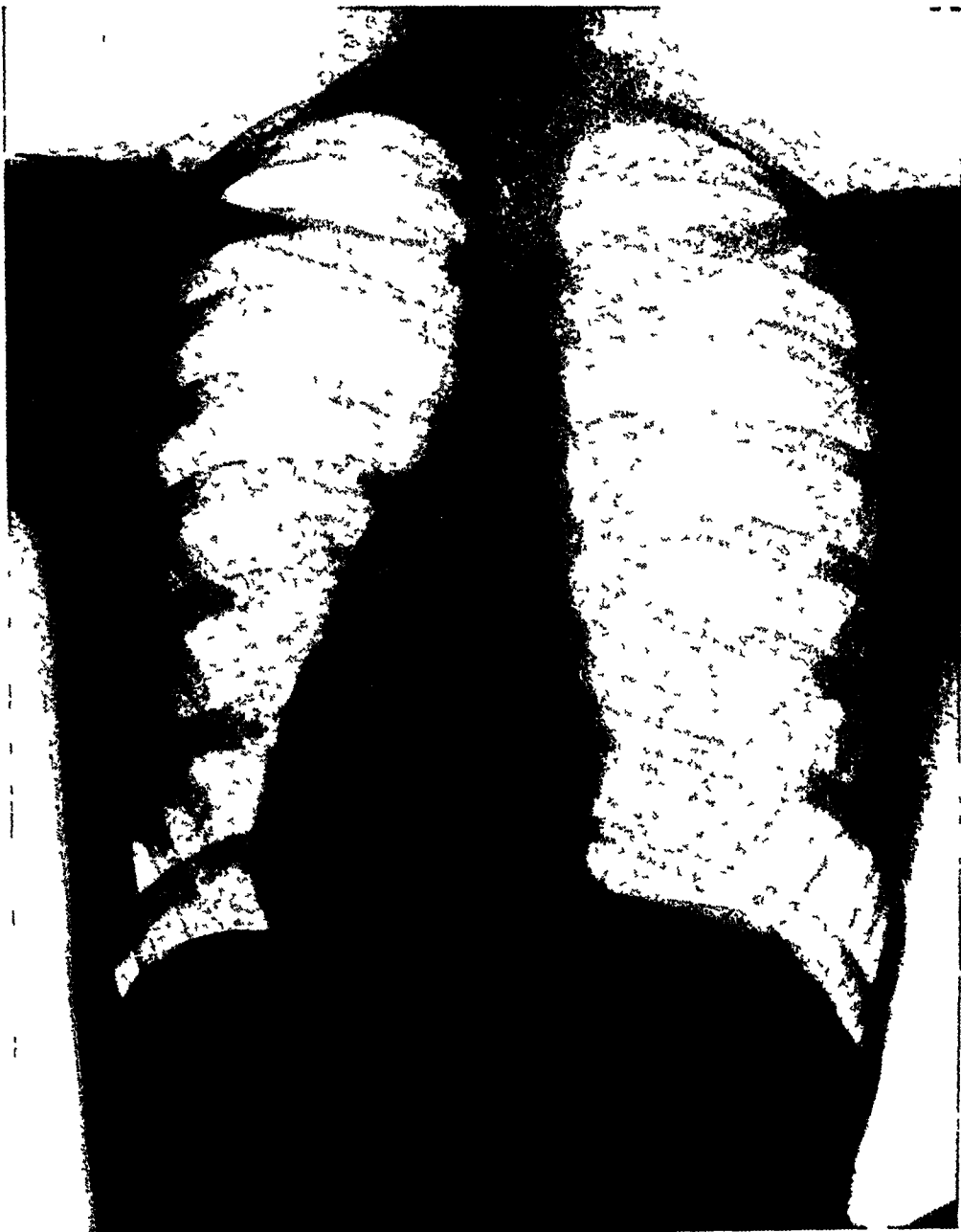
CASE 9 (R.M.) showing positive inhibitives in a Tb suspect. Serological diagnosis not proven correct till autopsy three years later (Part I, p 384)



CASE I Film I (S H ), 37548, June, 1928 Kindly forwarded by Dr W B Howes,  
Detroit Tb Sanatorium

*while continuously under my own observation* In six of these seven, I had stereograms of clear lung fields in the earlier months of observation, followed later by X-ray demonstration of definite parenchymal involvement

As periodic adjustment of terms seems necessary, so will it also be necessary here to define and qualify certain terms which heretofore have been rather loosely used by specialists, internists and practitioners alike



CASE 1 Film 2 (SH), T W H., July, 1928, by Dr W C Kreuger, Toronto Neither diagnostic of tuberculosis

Diagnosed first by serology three positive fixations, July-Sept., 1928 then tubercle bacilli found October, 1928 Complete history in Part I, p 383, case 1 (SH)

All *contact-cases* were known to have *associated with* a tuberculous patient who had tubercle bacilli in the sputum "Associated with" means more than a total of a dozen hours in the same unventilated room, with

the disease present but as yet undiagnosed, and the patient untrained Casual meeting out of doors or visiting on an open verandah is not counted as *contact* Recently, Alfred Henry<sup>13</sup> has very nicely defined, qualified, and

given examples of what is "known as a contact" and what is "not considered" such

For teaching and for charting purposes I have found it necessary also to estimate and qualify the size of the dose of infection available for inhalation or ingestion by the contact In talking to students or nurses I have referred to the daily, weekly or monthly dose of tubercle bacilli available for most city dwellers, as *minimal* If a worker at the same desk or bench, or a boarder at the same table, is discovered to have open tuberculosis, the dose of infection is spoken of as being *gross* If a room-mate, consort or fiancé, then the dose is *massive* The exposure under these three different circumstances could, in other terms, be spoken of as *casual*, *frequent* and *intimate*, respectively

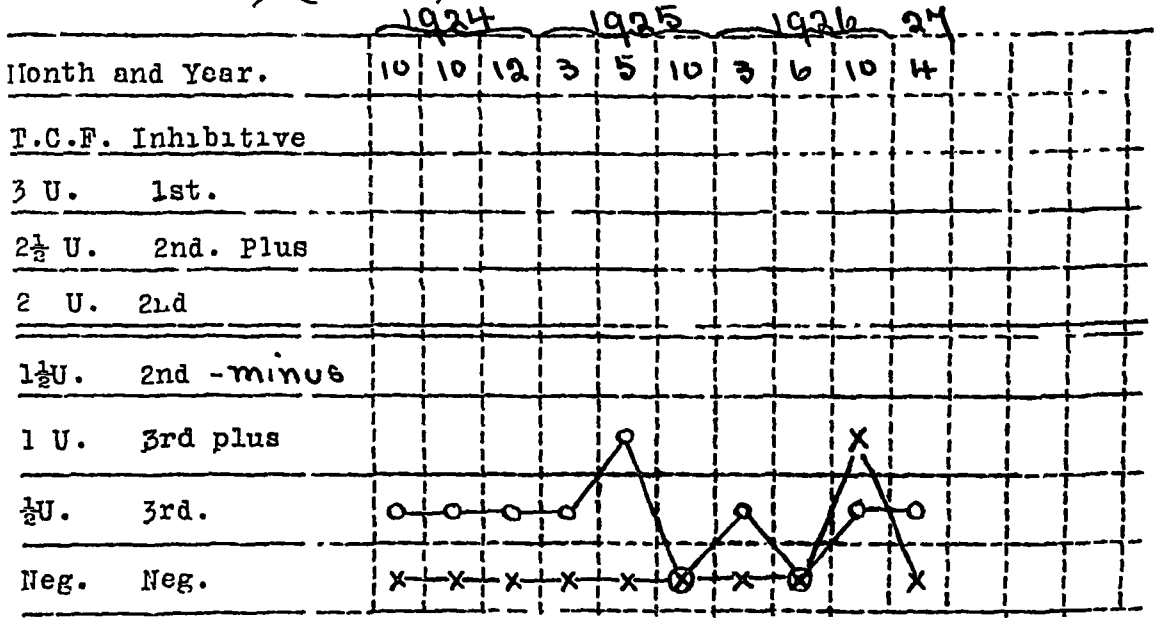
If we now were to attempt to estimate what these terms might correspond to in figures, say *tens*, *hundreds* or *thousands* of live tubercle bacilli, we should truly be making a rough guess Numbers need not concern us here as we are interested only in the relative size of possible dose

I have not yet been able to find a suitable single descriptive word for the *infecton*, the source of infection, the contaminator, the associate who is a careless or untrained open case of pulmonary tuberculosis

DESCRIPTION OF X-RAYS

The "Caulfeild-Richards"<sup>14</sup> (C-R) classification of stereograms of the chest" in use in the five X-ray laboratories most frequently quoted in these papers is adopted here as being, in our opinion, the most exact in anatomical

NAME *Example of the contact* .....  
*B.B. Case I (Hock)...*



Serial serological graph of contact  
CASE I (Hock) Showing both tests negative throughout

extent or volume of disease, and therefore the easiest to revisualize in the mind of the reader

### CONTACT-CASES WITH HISTORIES, SEROLOGICAL RECORDS AND X-RAYS

*Case 1* (Hock) Kept house for brother who coughed two years, and whom I sent to Waterloo County Sanatorium, August 1923, with B t present and classed according to X-ray "C-R extensive 1st degree" The sister, the contact-case was 'corralled' by me October, 1924 Graph herewith shows that I refused to believe her serum would not react till I had 10 double negatives and 2 clear stereotypes in 3 years (20470 Kruger) I had classed her as a contact to gross doses Would I have found positive reactions if I had tested her earlier than 14 months after exposure?

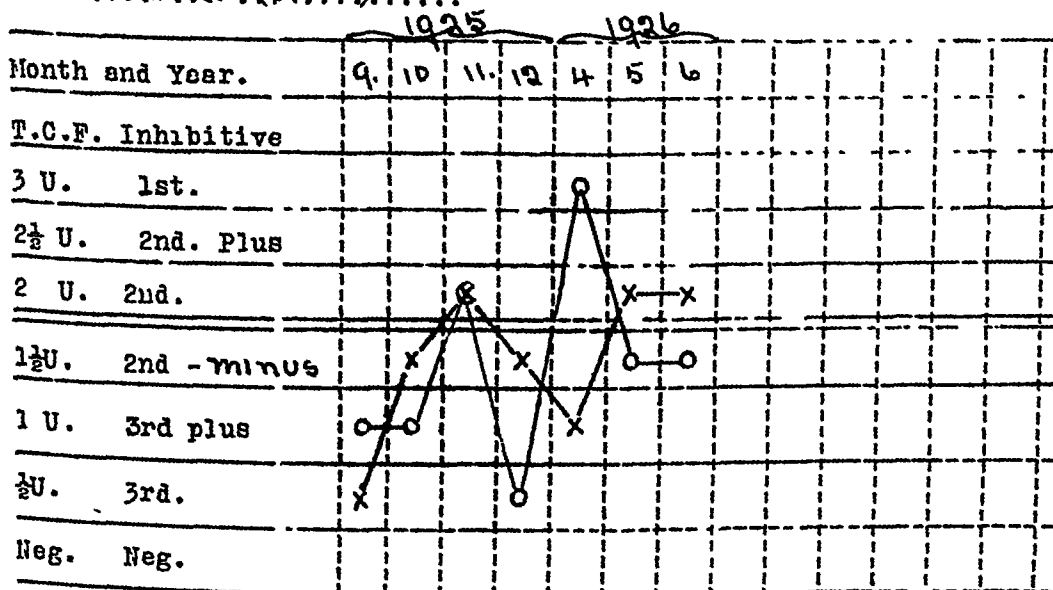
*Case 2* (H W) The wife of the contact was attended by me for four years and at her death in 1919 from Tb The husband-contact reported 1925, symptoms not

significant (Dr Wm Goldie) His graph herewith shows one or both tests positive in four of a series of seven This was 6 and 7 years after the last exposure which had ended in 1919 No lesion demonstrable in two pictures (Kruger T W H) Business removal interrupted observation

My colleague, Dr Caulfeild<sup>12</sup>, has been following one case with positive serological tests for 12 years in which at least two X-rays were negative until the last, when a clear cut minimal lesion was discovered in a practically symptomless man This is the longest time taken by a contact-case to develop a lesion, where the history is known to any of us and the case under continuous observation

*Case 3* (Z) Fiancé classed as X-ray "C-R intermediate 2nd degree" with cough and expectoration March and April, 1926, then sent to sanatorium by me Contact-case gave two 2nd class (positive) inhibi-

NAME *Example of T.b. contact...*  
P.P. *Case 2 (H.W.)*  
D.B. *Case 2 (H.W.)*



Serial serological graph of contact

CASE 2 (H W) showing positives in both tests

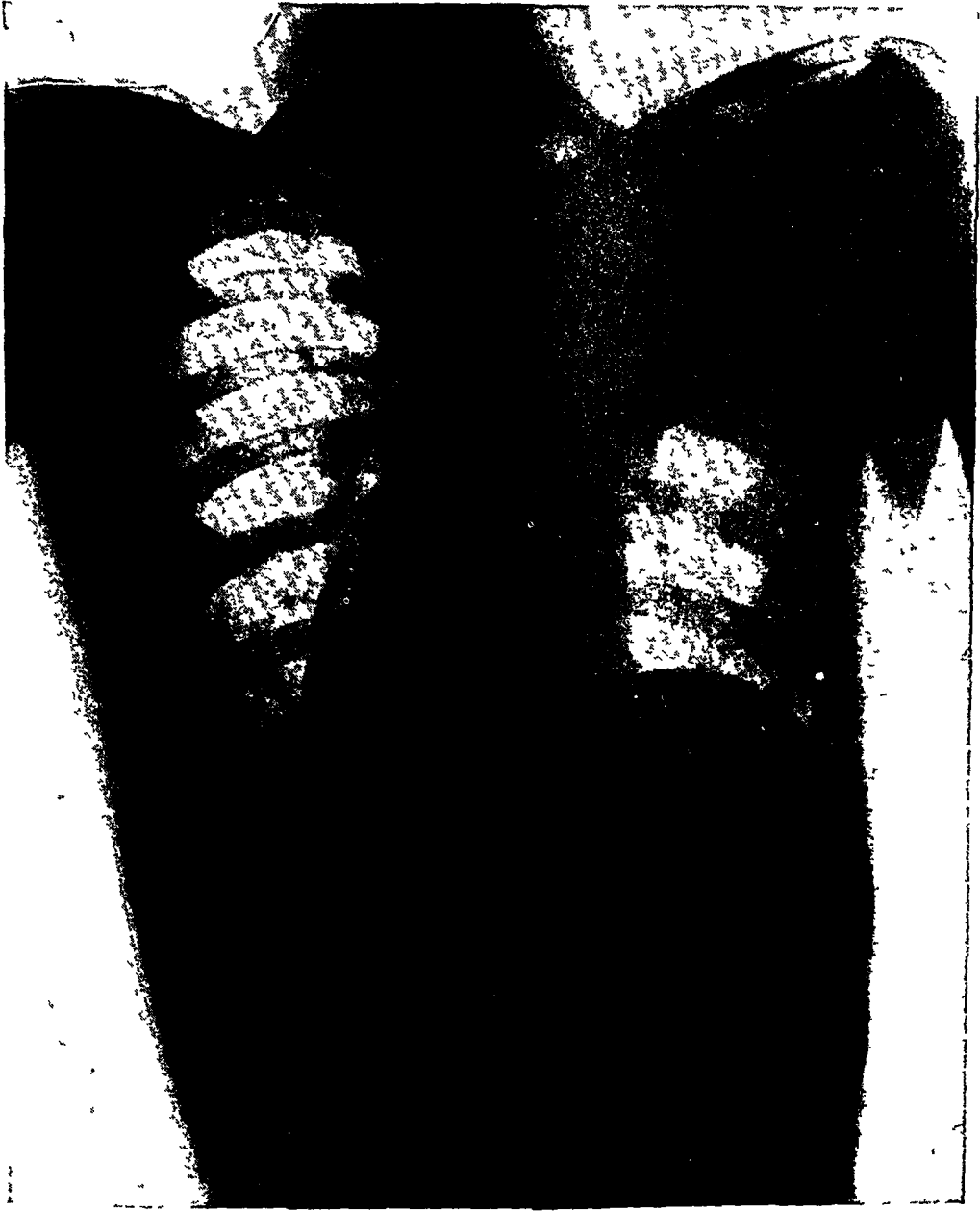


CASE 5 Film 1 (MNE) Jan, 1925 Three years after exposure Lesion beginning in right apex

tives and three two unit (positive) fixations in 4 double tests between September, 1926, and October, 1928 Two sets of stereos showed no lesion of parenchyma (Kruger) Contact-case seriously raised the question whether the alarm and restrictions were not worse than the possibility of the disease, wherewith I dropped the case

Case 4 (RE) Exposed to sister, who

was terminal case with positive sputum, and whom she nursed (both untrained) during the last 6 months of 1920, referred by Dr W R Campbell Stereograms of contact-case were clear (R4278, March, 1921, taken by Dr H M Tovell and kindly procured from his file for me six years later) A short series of three tests were within normal limits and so after 18 months observation



CASE 5 Film 2 (M N E ), 1925 Flared into tuberculous lobar pneumonia four months later

I discontinued, feeling further alarm unwarranted. She reported again, December, 1926, six years after exposure, having had 2 quarts of pleural effusion withdrawn, April of the same year (1926). Inhibitive now positive, steros (Dec, 1926, T W T 26273 and Q A Sanatorium, 4776, Jan 1927, kindly forwarded by Dr P M Andrus) showed "several light but definitely floccu-

lent shadows, peripheral zone, 1st and 2nd anterior interspaces and apices, both sides, less on the left, tuberculous (C-R minimal 1st degree). Referred to Dr John Oille for consultation.

Case 5 (M N E) This contact-case was exposed to gross and frequent doses, her father had active Tb, sputum positive, in the same house, 1922-23. Daughter-contact



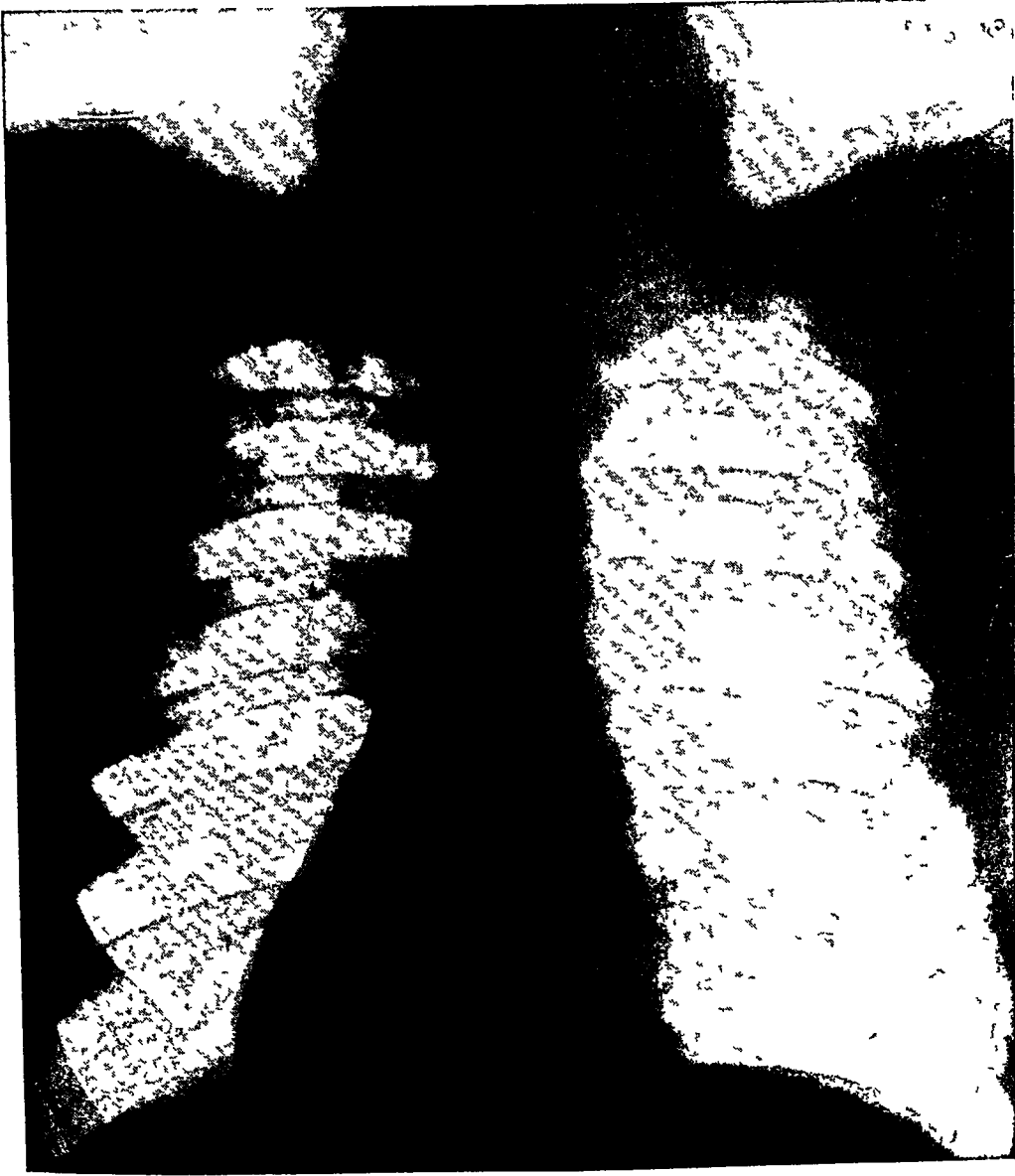


CASE 6 Film 1 (Pete) Dec, 1925 (20987) Brother's chest two months after exposure ended

was observed through 1924 but had no symptoms and no abnormal p's. Then fixation was positive in January, 1925, and I found impaired resonance and shower of fine râles in right apex, whereupon I ordered X-ray for the first time. Minimal parenchymal lesion was demonstrated in R apex, reproduced herewith. Sanatorium declined with a laugh, there being no symptoms. Four

months later, acutely ill with high fever. Dr. L. J. Solway diagnosed tuberculous lobar pneumonia. X-ray reproduced herewith. Sputum loaded with tubercle bacilli.

In relating the case at that time to Dr. Wm. Goldie and the late Prof. C. L. Starr, I had no X-ray corroboration of my negative clinical findings prior to



Lesion developing in brother twenty-seven months after tuberculous sister left for sanatorium

CASE 6 Film 2 (Pete), Feb, 1928, (33367) Brother's chest over two years after exposure ended

January, 1925, therefore no black and white proof that this date was the beginning of the lesion and the end of the incubation period. This decided me thereafter to order X-ray just within the 12 months after exposure, for two reasons: firstly, to have a picture of a clear chest for comparison in case a

lesion or suspicion developed later and secondly, to make certain that lesions were not developing earlier than I was looking for them viz 18 to 24 months. This rule I follow today in private and clinic practice.

Case 6 (Pete—spoke little English) was referred to T W H chest clinic December

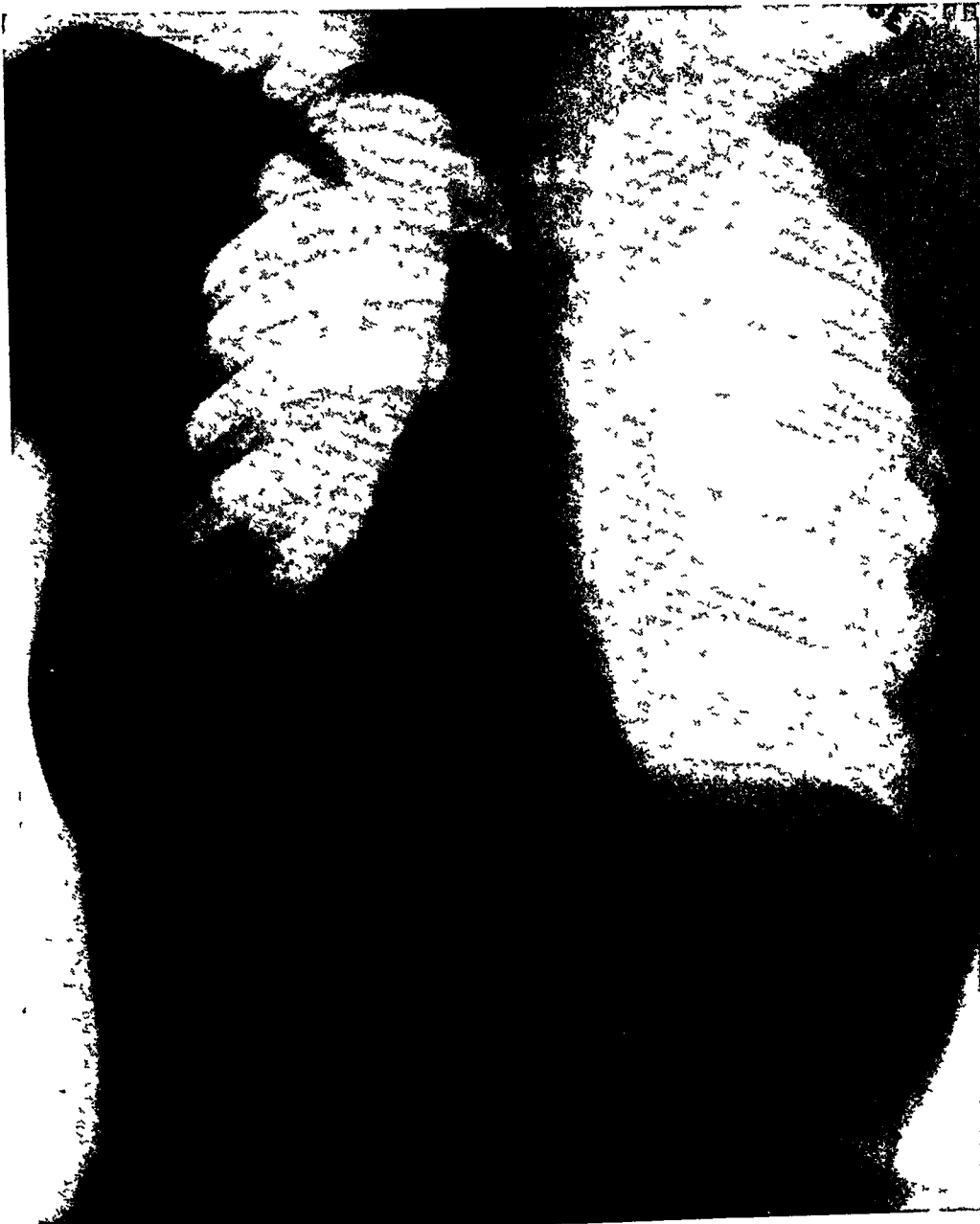


CASE 8 Film 1 (F D ) July, 1928 Twenty-five months after last intimate exposure

1925, as contact by P H nurse because I had reported his sister tuberculous He repeatedly denied living with, or going to see sister, he also reiterated that his sister had no cough With this history of doubtful exposure, clear X-ray picture (20987 shown herewith), and serology negative three times, I discharged him October, 1926, as being not an actual contact He reported

again February, 1928, with symptoms, positive serology and positive sputum, definite X-ray lesion (33367 shown herewith), viz, "C-R intermediate, 1st degree" Sent to Mountain Sanatorium

Again questioning the history concerning the possibility of exposure or actual contact, I received the same negative answers Surely he was giving me wrong answers, or I was



CASE 8 Film 2 (F D ) Sept, 1928 Twenty-seven months after last intimate exposure  
Tuberculosis flaring in third year after exposure

asking wrong questions! I changed my questions and received quite different answers

Q 1 'Had your sister a *hack*?

A 1 "Oh yes, she had little *hack*, often, but no cough"

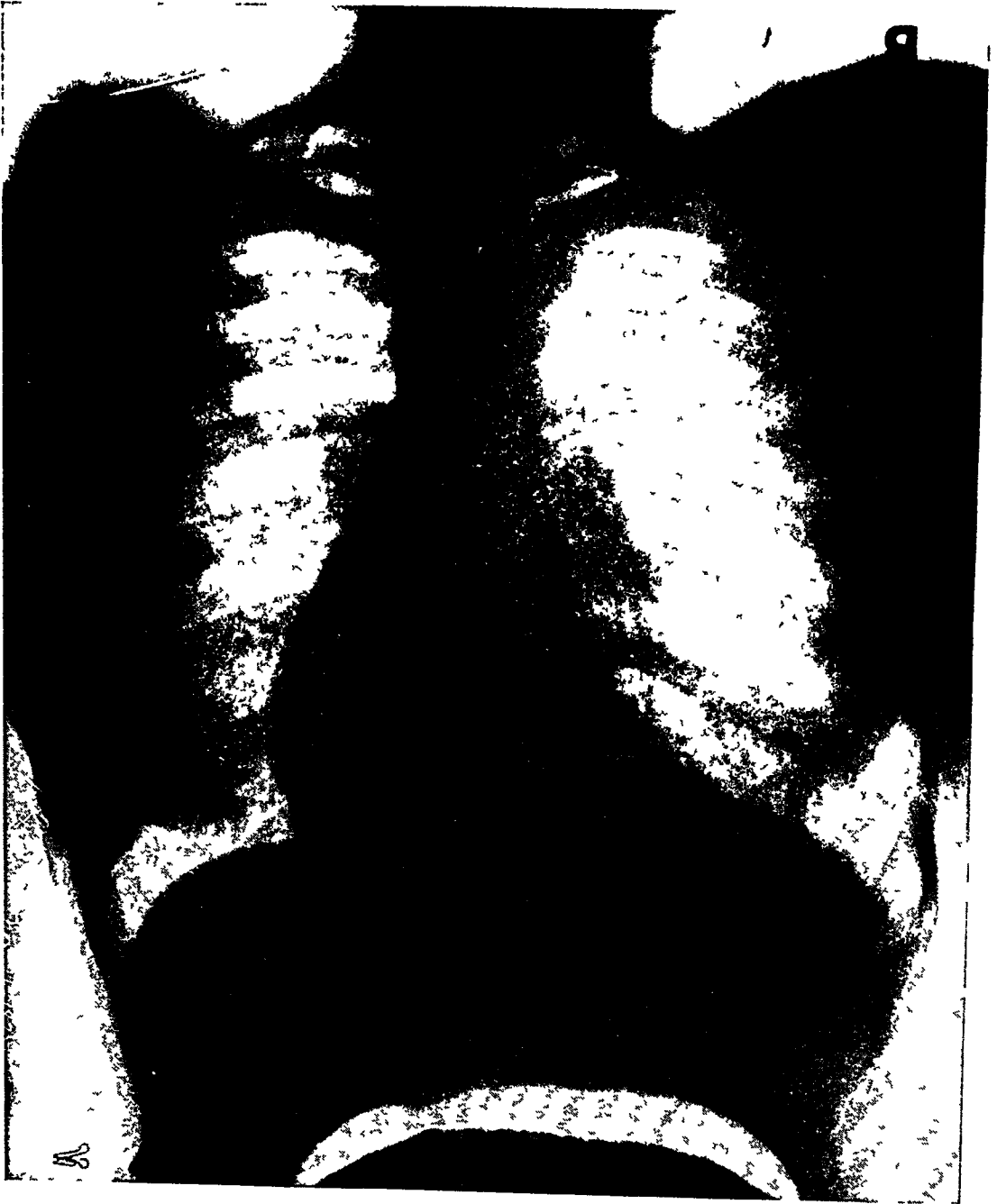
Q 2 "Did your *sister* go to see you?"

A 2 'Oh, yes, she came to my room three nights a week, eight to ten o'clock for

three months, summer, 1925 She have no sitting room I have'

I felt like a fool

Case 7 (M E) Was under observation because of frequent exposure in home of married sister with open Tb, 1920-22 During 1924 there was fatigue, 99.1°F and slightly enlarged thyroid which were not explained by a single B M R estimation

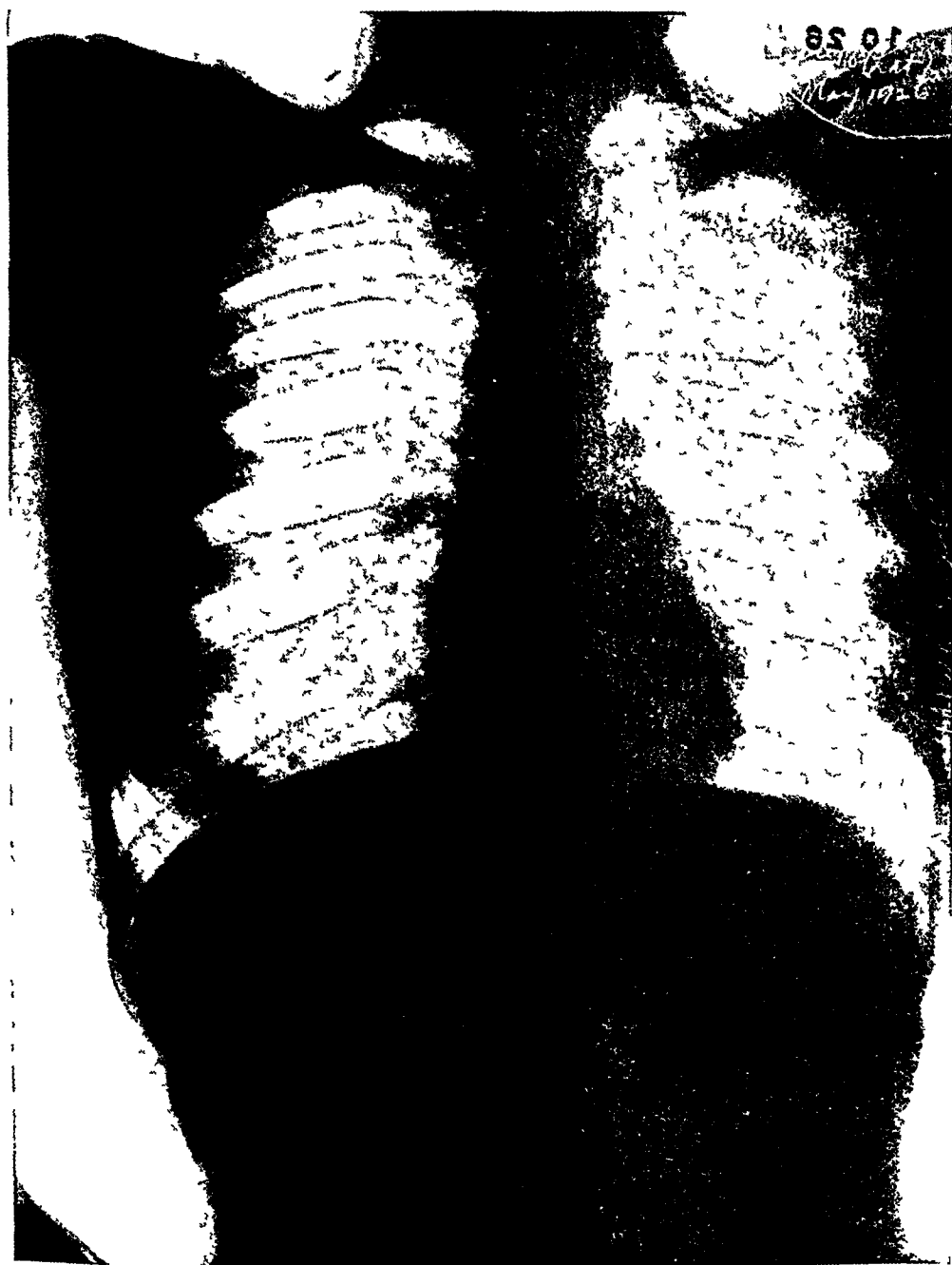


CASE 10 Film 1 (Lat) Nov, 1925 Nine months after exposure ended

A 2 unit (positive) fixation to tuberculo-antigens decided me (with some temerity) to send her to Freeport Sanatorium in June, 1924, although streos (T W H 15278) showed clear lung fields. As visiting consultant to this institution, I was enabled to observe the case each month. In September, Dr E. N. Coutts produced stereograms of a minimal parenchymal lesion half the width of a rib in diameter, (C-R minimal 1st degree) 2nd anterior interspace level, peripheral

zone almost as early as one could expect to catch a demonstrable lesion, particularly when watching for it.

Case 8 (F D) Lived with a sister who was an open case of Tb, January-June, 1926. She then entered training school for nurses. She was observed as a contact through 1927, X-ray clear in December and several blood tests within normal limits. Convinced as we were that this girl had been an *actual* contact, we were disappointed that certain



Demonstrating the shortest incubation period in our series observed by X-ray  
CASE 10 Film 2 (Lat ) May, 1926 Fifteen months after exposure ended

contingencies interfered with regular monthly serological tests<sup>3</sup> we might have caught a biological reaction that would have warned us sooner of what was coming, that is, before it was too late. A second stereogram July 17 1927 showed nothing definite (reproduced here) but inhibitive was positive, whereupon Dr George C Anglin ordered

her home to bed. Next month, while still in bed, there was troublesome spasmodic cough with expectoration and fever, not seen by physician. When I visited her, thirty miles away the following month, September, I found profuse rales over left upper half, front and back not in themselves diagnostic of tuberculosis. Three sputum

examinations were negative, and I ordered her to town for X-ray September 28, 1928 (reproduced here) Tuberculous lesion shown throughout left upper Tubercle bacilli found in sputum at Muskoka Hospital Feb 13, 1929 (Reported by Dr C B Ross)

We have too frequently seen that if a nurse breaks down with tuberculosis during training, the family blames the hospital and in particular the lady superintendent. The physician to training schools can no more suspect potential tuberculosis without history of contact than can he detect epilepsy by physical examination. I have therefore taken the stand that superintendents of training schools cannot afford to accept actual contacts as probationers, and in the autumn of 1928 I so advised Miss Beatrice Ellis, Toronto Western Hospital.

*Case 9 (K)* Consort was referred by Dr Geo S Young, autumn 1925, for disposal, because of active Tb, and was sent to sanatorium for six months. In March, 1926, when the contact gave positive inhibitive but clear X-ray (5009 Richards), my request to report periodically was declined. Over two years later, in August, 1928, was twenty pounds heavier and symptomless when a free hemoptysis occurred. On auscultation I heard, following a cough at the end of forced expiration, a shower of râles over the right upper two spaces anteriorly, and stereograms (10202 Richards) showed a definite lesion in this area.

The only thing in addition which I might have done, was to have tried the effect of giving the contact one of my appointment cards to report for periodic observation—a system introduced and in common practice by a sister profession and accepted much more readily by the laity than is the case in medicine. They have their patients better trained than have we.

At this particular time another contact was under desultory observation, in fact apparently had stopped reporting. With the crash of case No. 9 more or less on my medical conscience, I decided to try the appointment card scheme, sending a letter with it. It resulted in only one more consultation—see case No 3 (Z) above (And both of these were active members of my own profession!)

*Case 10 (Lat)* The husband was diagnosed tuberculosis throughout R lung (C-R extensive 1st degree) February 1, 1925, and transferred to sanatorium until decease January, 1926. He had coughed since September, 1924. The wife-contact gave two units of complement fixed twice in 1925, stereos clear May, 1925, and again November, 1925, the latter (Kruger) reproduced herewith. Because of suspicious p.s., May, 1926, but with no complaints, Dr Caulfield referred her for stereogram, demonstrating lesion the size of tangerine (C-R minimal 2nd degree) in left upper, reproduced herewith. The incubation period was a minimum of 15 months, the exposure ended January 31, 1925. The remainder of the household were clear.

This fifteen months incubation period was the shortest in our series. The lesion might have been demonstrable by X-ray in twelve months, it certainly was not in nine and the contact was observed while she was under fairly strenuous working conditions.

Because of this revelation, if a contact is necessarily under similar social conditions, I feel safer in repeating stereograms every three months starting at twelve months after exposure.

#### COMMENT

Believing from observation that the tests were specific, these investigations commenced with an attempt to find

whether those recently in intimate contact with infective tuberculosis would react biologically, as indicated by the TCF and the Inhibitive. The examples given go to show the value of the tests in contacts

In attempting to classify some 200 contacts in private practice (and the same proportions would hold good in another 200 in clinic practice), there were four main groups

Group I, the largest, were those who gave positive tests for two years or more and did not develop lesions

Group II, the second largest, were those giving negative tests, also with no lesions

Group III were those whom we did not see till two, three or four years after exposure, then, finding positive tests, we X-rayed and found lesions without apparent activity

Group IV were those who developed lesions while under observation, always anticipated, (where closely followed) by positive tests

The latter two groups, III and IV, were about equal in size

It was thought that the findings in this ten year period were sufficient to stimulate the more active interest of others, even in face of the several difficulties mentioned

It would seem that a provincial or state department of health may be willing to provide these tests, if we could guarantee equal use to urban and rural practitioners alike. For the latter however, time and transportation interfere, certain changes in the serum, too often occur, interfering with the reliability of the reactions. Dr Arthur C Norwich<sup>15</sup> of the D P and N H has recently made some modifi-

cation of the technique with a view to eliminating possible false reactions

In 1912 I "hoped that the closer investigation of *suspect* tuberculosis would soon be available for the many rather than for the few"<sup>16</sup> Eight years later in 1920, although I did not anticipate Part II of the present paper on *contacts*, I did forecast<sup>3</sup> the name of Part I "It is therefore satisfactory to have further definite assistance in diagnosis (by serology), even to the point of being able to recognize the disease in the *pre-clinical* or *biological* stage, and with this advance information, and by treatment, or restricted routine, to be able to keep the patient from reaching the stage of symptomatic tuberculosis"

#### SUMMARY

1 Greater effort should be made, by more accurate history taking, to estimate the dose of tubercle bacilli received by contacts

2 Some such classification as minimal, gross and massive contact, or casual, frequent and intimate exposure, is submitted

3 Most "intimate" contacts have been found to react serologically for two years or more after the exposure

4 A minority of adult contacts to open tuberculosis have been found to develop lesions when observed into the third or fifth year. The exact percentage is at present undetermined and so far, has been difficult to estimate

5 Contacts should be kept under observation for a longer period than was heretofore considered necessary

6 Superintendents of training schools for nurses should not admit



recent intimate contacts as probationers

7 Medical directors of insurance companies might well postpone insurance to recent contacts unless they have assurance of such financial standing and mental make-up as would guarantee against stress

In addition to those mentioned in Part I, my appreciation is due Dr G C Anglin and Dr T R Welwood, my associates on the T.W.H. Chest Clinic for the past ten years, my confrere Dr E N Coutts, Medical Superintendent, Freeport Sanatorium, and to the Board of Directors of the latter institution for their confidence and support since 1921 in the working out of some of these problems

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# Some Observations as to the Results of Phrenic-Exeresis in Pulmonary Tuberculosis\*

By LIEUT COLONEL A T COOPER, M C, *U S Army*

**A**VULSION of the phrenic nerve has been used as one of the agencies in collapse therapy for treatment of pulmonary tuberculosis at Fitzsimons General Hospital since approximately 1922

Notwithstanding the fact that this operation has been of record in medical annals since 1913, the Staff at this Hospital, previously to 1922, felt some reluctance in recommending it, because the ultimate result as to the thinning and paralysis of the diaphragmatic muscles with the extent of the ascent of the upper abdominal viscera into the thoracic cavity, was unknown. It was feared with complete and permanent paralysis of a diaphragmatic leaflet, that a considerable eventration of the upper abdominal viscera might take place. By carefully watching, over a number of years, patients who have had this operation, it was shown that no marked eventration takes place, and the fact was demonstrated, that even in the permanently paralyzed diaphragm, a rise is not excessive and is limited.

There is one case, however, which would be well to mention at this point—where a patient having a large cavity

in his left lung, refusing any operative procedure other than phrenic-exeresis, was eventually operated upon. During the progress of the disease, the whole of his left lung practically excavated. The left leaf of his diaphragm ascended about half way into the thorax, and along with this went the underlying viscera, that is, the stomach, and part of the colon. This man experienced rather disturbing gastro-intestinal symptoms, but eventually consented to a thoracoplasty on his left side. This is to be done in stages, so that the left side of his thorax is in the process of being totally collapsed, and he has since experienced a great deal of amelioration of his gastro-intestinal symptoms, which were not only incident to excessive cavitation in his left lung, but also were possibly due to the rather high position of his stomach and likely the colon.

As we have come to be more familiar with the results of this operation, we are becoming more liberal in recommending it, not only because of the ease and the lack of danger, which attends it—it can, in most cases be done under local anesthesia—but also because of the large per cent of patients, who in one way or another, derive considerable benefit from it. One

\*From The Medical Service, Fitzsimons General Hospital Denver Colo

benefit derived from this operation is that the work of the lung on the side on which operation was done, is lessened. This is demonstrated even in cases where there is no rise in the diaphragm by a definite lessening of the respiratory mound over the base of the lung on the side operated upon. This phenomenon is more or less constant in all cases in which phrenic-exeresis has been done. Immediate result of the operation is, as a rule, a definite lessening of any pleuritic pains and discomfort which may have been present on the side from which the nerve has been avulsed. Slight discomfort may be complained of for a few days at the site of the operation and extending over the tract of the phrenic nerve, but this is minimal and of no consequence. After a few days, the patient generally definitely remarks that his cough is not so distressing, that although he may raise the same amount of sputum as he did prior to the operation, it is raised with less distress and effort. No comment on this phenomenon can be made with the data available. In a few days there is usually a noticeable rise apparent in the diaphragm on the side on which operation has been done, and this may increase up to a distance of six to seven centimeters in two or three weeks, or several months may elapse before the ultimate ascent has been reached.

The object of a phrenic nerve operation is to definitely lessen the aeration of the lung on the side operated upon, by paralyzing the corresponding half of the diaphragm. This paralysis, permitting the diaphragmatic leaflet to rise, partially compresses the lung. Therefore, phrenic-exeresis is one of

the procedures to be used in collapse therapy. Some patients will accept this operation when they will accept no other form of collapse therapy.

If a complete avulsion is done, and 14 to 15 centimeters of the nerve removed, paralysis is usually complete. If but a small section of the nerve is cut out, the paralysis is only temporary. It has been reported that even in the avulsion of as much as 14 or 15 centimeters of the nerve, occasionally anomalous nerve branches have re-established motor activity of the entire diaphragm.

The definite pumping, and possibly the tearing action of the diaphragm on pulmonary lesions in cavities in the lower part of the lung is considerably lessened by paralysis of this major muscle. We have found that even where there are extensive adhesions between the lung and the diaphragm, or between the visceral and parietal pleura in the lower part of the lung, an extensive rise of the diaphragm may result and be of benefit to cavities and lesions particularly in the central and lower part of the lung. This was definitely shown in one patient upon whom phrenic nerve operation had been performed with good results, and subsequently in order to completely collapse the cavity in the apex posteriorly, thoracoplasty was done. Several days after the latter operation, the patient died of embolism of the pulmonary vein of undetermined etiology. On post mortem examination it was found that even in spite of the extensive adhesions between the diaphragm and the lung pleura, and also laterally between the parietal and visceral pleura, an excellent rise had been obtained, the dia-

phragm having risen from six to seven centimeters

It has also been noted that phrenic-exeresis may be of definite benefit in closing cavities and healing lesions not only generally throughout the lung, especially in the lower and central regions, but also occasionally in the upper portion as well. Even where there is considerable amount of uninvolved lung tissue between the diaphragm and a cavity in the upper part of the lung, following a phrenicectomy, the lower healthy lung seems not to be compressed so much as to rise with the diaphragm and to compress the more diseased upper portion of the lung.

The indications in general which are followed in this hospital in recommending a phrenic nerve operation are where the lesions show definite retrogression in one side either with or without cavitation, and the lesions in the contralateral lung are minimal, with little or no cavitation present, pneumothorax being impracticable or having been tried unsuccessfully. However, it is difficult to find ideal cases, and if the internist delayed waiting only for ideal cases before making a recommendation for phrenic-exeresis, such recommendations would not be made in the majority of cases, and many patients who might derive a great deal of benefit from such an operation, would not be operated upon.

Phrenic-exeresis may be done as a sole procedure, but in most cases it is done in conjunction with other methods of collapse therapy. We have used it in conjunction with pneumothorax, as a preliminary step to thoracoplastic operations and subsequent to thoracoplasties. Phrenic-exeresis is

indicated and should be done on patients in whom pneumothorax being indicated, has been unsuccessfully attempted. It is both inadvisable and hazardous to attempt pneumothorax more than three or four times. With the presence of extensive pleuritic adhesions, there is always danger in attempting pneumothorax of producing air embolism which is a very serious complication. No more than three or four attempts at pneumothorax should be made, when if unsuccessful phrenic-exeresis should be seriously considered. Pulmonary lesions limited to the central or lower part of one lung are a definite and positive indication for phrenic-exeresis. Most of such cases received marked benefit not only in their symptoms but also in providing a permanent collapse therapy to diseased pulmonary areas. Painful and persistent pleurisy in the lower part of the lung, with hiccough or pleuritic pain, is also an indication for phrenic nerve operation. Pleuritic pain is lessened in patients with such complications after operation.

Preliminary to thoracoplasty—where a complete collapse of one lung is desired and several stages of thoracoplasty are contemplated phrenic-exeresis may be done, as this will in many cases, lessen the number of ribs which it is necessary to resect in order to obtain a complete collapse, and so produce less thoracic deformity. Where a complete thoracoplasty is not contemplated in many cases phrenic-exeresis is advisable in order to partially collapse the lung on the side to be operated on, as a preliminary measure and to test out the opposite lung. Such a test will often give the clinician an

idea as to how well the contralateral or minimal involved lung is going to react to a thoracoplastic operation on the most diseased side. In all probability phrenic-exeresis is of value in possibly preventing paradoxical or pendulum breathing subsequent to thoracoplastic operations. This complication is a decidedly serious one following operations on the chest, and phrenicectomy may be of help in preventing it.

The contraindications are of course extensive—bilateral pulmonary disease particularly, where there is rather extensive bilateral cavitation, although we have not hesitated even in terminal cases with distressing cough and pain on the most involved side due to pleurisy, to recommend phrenicectomy, where chest pain can possibly be lessened, and where it is thought that the patient would be made more comfortable by lessening his distressing cough and enabling him to eject his sputum with less effort.

Cases with marked bilateral emphysema or asthma are not good cases for phrenic-exeresis. In military tuberculosis, extensive throughout both lungs, of course no benefit can be obtained. Cardiac and renal diseases are not considered contraindications, if not advanced.

Since 1922, this operation has been performed on approximately two hundred patients at this hospital, and in studying a portion of these patients, it was found that approximately 70% of those operated on the right side showed definite rise, while on the other hand only 55% of those who were operated on the left side, showed definite rise. This observation was made after care-

ful comparison of preliminary X-rays and plates following operation, and shows that there are greater chances of a more successful result following operation on the right side than on the left, if success is to be measured by a rise in the diaphragm. Yet we have found that a rise in the diaphragm is not the sole criterion for successful results. Many patients, who showed no rise, yet as a result of diaphragmatic paralysis as shown by fluoroscopic examination of the diaphragmatic leaflet, showed definite improvement as far as tending to clear up the pulmonary lesions was concerned, and this is to be explained only as a result of a definitely paralyzed diaphragm which lessened pulmonary ventilation and action, as there was no apparent resultant vertical compression of the lung.

The question of gastrointestinal disturbances following exeresis has been raised, and while there are approximately 40% of the cases who have symptoms, from slight to rather marked, persisting for two or three weeks, these symptoms have not been such as to interfere with their digestion and have subsided after a few weeks time.

It may be well finally to mention an unfavorable termination in a case of pulmonary tuberculosis on which a left phrenic-exeresis was done, because it was thought that a midlung cavity was present on that side, but which eventually was determined to be a localized spontaneous pneumothorax. A good rise of the left diaphragm resulted. Subsequently, due to a large apical cavity on the right, an upper stage thoracoplasty was recommended and done on this side. Immediately upon

completion of the thoracoplasty, the patient developed paradoxical respiration and died shortly. From this one case, it would appear that thoracoplasty is a hazardous procedure, if phrenic-exeresis has been done on the opposite side.

In studying the effects on cavities, it has been noted that cavities in the midlung or base, are more apt to be benefited by a phrenic-exeresis than are cavities higher in the lung or in the apex. A tendency toward compression has been noted in about 42% of the cavities in the midlung or base, while only 30% of the cavities higher in the lung than the central part have been noted to be definitely benefited.

The same is true of involvement in different parts of the lung, even without cavitation. It is well to remark here that phrenic-exeresis is not a panacea, even for basal cavities or basal involvement, as we have noted in one case having a cavity low in the base of one lung on which phrenic nerve operation was performed, that no benefit was derived from the operation, the cavity continuing to enlarge notwithstanding a definite rise in the diaphragm.

#### SUMMARY

I Phrenic-exeresis is of value in many cases of pulmonary tuberculosis where the lesions are mainly unilateral.

II Beneficial results have been noted even where there is no corresponding rise in the diaphragm.

III A good rise of the diaphragm may ensue even with the presence of adhesions.

IV Phrenic-exeresis is particularly indicated in unilateral cavitation involving the lower or central part of one lung.

V Phrenic-exeresis is indicated where attempt at inducing pneumothorax is unsuccessful.

VI Phrenic-exeresis is useful as a preliminary step where complete thoracoplasty is contemplated, as sufficient collapse may be obtained with resection of fewer ribs and less deformity, also it is useful as a preliminary procedure in many cases to test out the contralateral lung.

VII This operation frequently ameliorates much of the distressing and wracking cough present in far advanced cases and enables the sputum to be raised with less effort.

# Primary Tuberculosis of the Spleen: Its Clinical Resemblance to Banti's Disease.

## With a Report of Three Cases\*

By ALVIN E PRICE AND RONALD L JARDINE. *Detroit*

**S**ECONDARY involvement of the spleen in cases of generalized tuberculosis is not rare. Griffin<sup>1</sup> has estimated its occurrence in twenty per cent of adults, while in children he regards it about three times more frequent (50-66 per cent). Others would place these figures still higher, regarding the incidence close to one hundred per cent. "Primary Tuberculosis of the Spleen" on the other hand, as described by Auché<sup>2</sup>, Bayer<sup>3</sup>, Block<sup>4</sup>, Ciaccio<sup>5</sup>, Léon-Kindberg<sup>6</sup>, Quéne and Baudet<sup>7</sup>, Sotti<sup>8</sup> and others, is found to be much less common. Winternitz<sup>10</sup> in 1912 reviewed some fifty-one cases reported up to that time and since then about half again as many have been reported.

By the term "Primary Tuberculosis of the Spleen" is implied the localization of the process in this organ to an extent which is greater than that found in any other part of the body. It does not necessarily mean, that the spleen is the portal of entry of the infecting organism, nor does it preclude the existence of others tuberculous foci in the body (Klotz<sup>9</sup>).

During the past year we have had the opportunity to study three cases which have come under observation in Harper Hospital. In all three a pre-operative diagnosis of Banti's disease was made, and it was not until subsequent laparotomy with microscopical study that the tuberculous nature of the condition was recognized. In view of the mistaken diagnosis in all three cases, we became impressed with the clinical similarity existing between primary tuberculosis of the spleen and Banti's disease, and concluded that it would be of interest to report the cases from this standpoint.

*Case 1 History.* A P, adult male, age 41, was admitted to the medical service of Harper Hospital on April 15, 1929. His illness started about six months prior to his admission with generalized weakness and pain in the U L Q. Somewhat later he had profuse night sweats. The physician consulted at that time instituted a course of X-ray treatments over the spleen, this resulting in some improvement in the patient's general condition. Several months later, however, the weakness returned and the patient was admitted to a local hospital. At this time the spleen and liver were both found to be enlarged, the former extending to the iliac crest, and the latter to ten centimeters below the costal margin. The blood picture was as follows—Hemoglobin, 42%,

\*From Harper Hospital, Detroit, Michigan

RBC 2,250,000, WBC 1950 PMN, 26% SL 18% Eos 2% and Myelocytes 54% A diagnosis of chronic myelogenous leukemia with marked anemia and leukopenia (secondary to X-ray therapy) was made, and a series of eight blood transfusions was given Following the latter, the hemoglobin became 60%, the red count rose to 3,200,000 and the white count increased to 7,100 All myelocytes disappeared from the blood stream The general condition of the patient then improved, although no difference was noted in the size of either the liver or the spleen Shortly after his discharge from the above institution he was admitted to our hospital, his chief complaints being "weakness and a mass in the abdomen"

The family and past medical history were negative

*Physical Examination* The patient was moderately well developed and poorly nourished having a peculiar "muddy" tint to the skin The eyes were somewhat sunken in their orbits The mucous membranes of the mouth were pale, without pigmentation The chest was symmetrical with definite depression of the supra- and infra-clavicular fossae Resonance was impaired high in the left axilla Breath sounds were exaggerated over both upper lung fields and a few fine crepitant râles were heard over the left base posteriorly Heart was negative except for a systolic murmur at the apex BP 90/50 Abdomen—rotund and tense with evidence of fluid The spleen extended well below the umbilicus and medially as far as the mid-line The surface was hard and slightly irregular on palpation The liver extended two finger breadths below the costal margin Extremities—negative

*Laboratory Data* Blood Count (4/22/29) HB 70% RBC 3,680,000 WBC 6,000 PMN 85% SL 11%, LL 4% Red cells showed some poikilocytosis Reticulated cell count 7% Platelet count 650,000 Bleeding time 2 mins Coagulation time 4½ mins Blood Wassermann and blood sugar—normal Blood nitrogen 40 mgs per 100 c c Urinalysis—negative except for urobilinogen

Liver function test—Van den Bergh reaction—direct—neg, indirect—weakly positive Icteric index 4 Bromsulphalein dye

test—negative Levulose tolerance test—negative

X-Ray—Lungs—negative for evidence of tuberculosis

*Clinical Course* While in the Hospital, the patient complained of weakness and abdominal discomfort,—the latter due to pressure from the enlarged spleen The temperature varied between 100.4 and 101.6, the pulse between 80 and 120 On the basis of the above findings, a clinical diagnosis of Banti's disease was made and splenectomy decided upon At the operation the spleen was found to be enormously enlarged and adherent to all the surrounding structures by easily separable adhesions The neighboring tissues showed signs of acute inflammation Free fluid was found in the abdomen and the liver was slightly enlarged

On the day following the operation, the temperature rose to 102, the pulse to 140, and the patient expired Permission for autopsy could not be obtained

*Pathological Report* Spleen measured 30 cm in its longest diameter and showed numerous large wedge-shaped areas of caseation necrosis on its surface and on cut section (Figure 1) Microscopic examination revealed marked thickening of the splenic capsule Throughout the pulp were myriads of miliary tubercles in various stages of development,—some already undergoing caseation Farther removed from the capsule were large caseous areas surrounded by avascular epithelioid zones with many multinucleated giant cells (Figure 2)

*Pathological Diagnosis* Active Chronic Tuberculosis of the Spleen

*Case 2 History* D H, white female, age 41, was admitted to Harper Hospital Nov 16, 1929, complaining of weakness and a mass in the upper part of the abdomen In 1919, when the tumor was first discovered, the patient was submitted to an exploratory laparotomy, after which she was told that she had an "enlarged spleen and a large fibrous liver" During the following year, a course of X-Ray treatments was instituted but without apparent effect on the size of either the spleen or liver The general condition of the patient remained unchanged until April 1929 (seven months prior to her



admission to our hospital), when she started to lose weight, became weak and had frequent night sweats. There was also an occasional afternoon fever, but no cough.

**Physical Examination** The patient was well developed but poorly nourished, having a definite pallor combined with a faint icteric color to the skin. Eyes—negative except for slight icterus of sclerae. Lungs—negative for evidence of tuberculosis or other pulmonary disease. Heart—negative. B.P. 108/68. Abdomen—There was a large, smooth and slightly tender mass in the U.L.Q.—extending to within 2.5 cm of the iliac crest and well over the midline. Liver was enlarged to five finger breadths below the costal margin. The surface was smooth and firm. No ascites was demonstrable. Extremities—negative except for slight tenderness over right tibia.

**Laboratory Data** Blood Count (11/16/29)  
Hb, 60% RBC, 3,360,000, WBC, 2,950, PMN, 48%, L, 43%, M, 2%, Eos,

7% Blood Wassermann—4 plus Blood N. CN, 26 mgm Blood Sugar, 0.87 mgm Blood fragility—beginning hemolysis 45% Complete hemolysis, 35%

Urine—negative No urobilinogen

Van den Berghs—direct—slightly positive, indirect—positive

X-Ray of chest revealed an increase in lung markings in left base, but no definite parenchymal lesions.

**Clinical Course** During her stay in the hospital, the patient had a daily afternoon temperature elevation of 100°. On the third day one X-Ray treatment was given over the spleen. Two days later, a direct blood transfusion (300 cc) was done, followed in two hours by splenectomy. The preoperative diagnosis was Banti's disease.

At operation, the spleen was found to be hard in consistency and about six times its normal size. The liver was also markedly enlarged. No free fluid was seen in the abdomen.

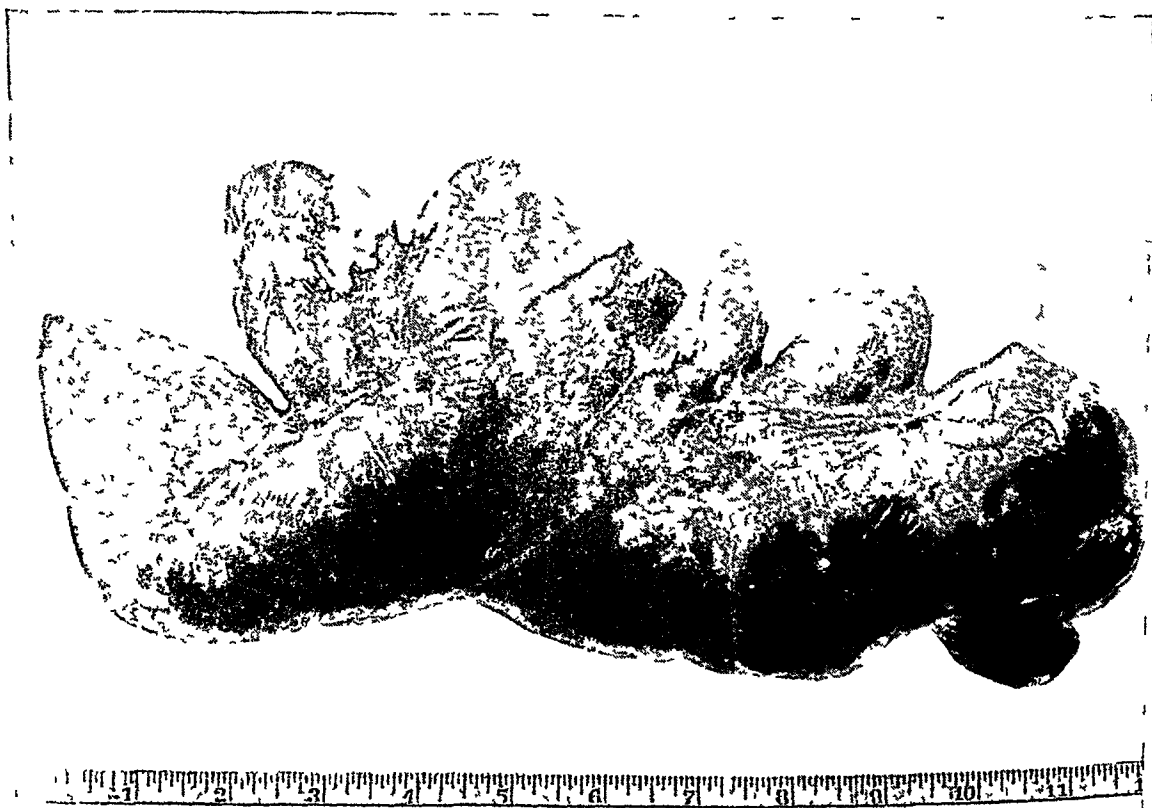


FIG 1 Spleen showing wedge-shaped area of caseation necrosis on cut section

On the third day post-operative, the patient died. Permission for autopsy could not be obtained.

*Pathological Report* Spleen was enormously enlarged and firm in consistency. On the anterior surface, there was a large area of caseation necrosis (Figure 3). Microscopic examination revealed large areas of caseation surrounded by an avascular epithelioid zone. There were very few giant cells. Recent disseminating miliary tubercles were found throughout the splenic pulp in the zone outside of the caseous areas (Figure 4).

*Pathological Diagnosis* Chronic caseating tuberculosis of the spleen with recent dissemination.

*Case 3 History* G. A., white female, age 33 yrs, was admitted to Harper Hospital Aug 8, 1929, complaining of weakness, tumor in the abdomen and a loss of nine

pounds in weight. The abdominal tumor had been noticed for the first time about one year previously, and since that time had increased in size gradually. There was no history of fever, night sweats, cough, jaundice or hematemesis. Amenorrhea had been present for six months.

*Physical Examination* The patient was poorly nourished and poorly developed with evidence of recent loss of weight. Eyes—no icterus of sclerae. Lungs—breath sounds bronchovesicular in type with fine râles at both apices. Heart—negative. B P, 120/75. Abdomen—there was a large, freely movable mass in the U L Q, extending to the iliac crest below and to the midline medially. Surface was smooth and firm. Liver—not demonstrably enlarged. There was moderate ascites. Extremities—negative.

*Laboratory Data* Blood Count (8/8/29) Hb, 70%, R B C, 4,420,000, W B C,

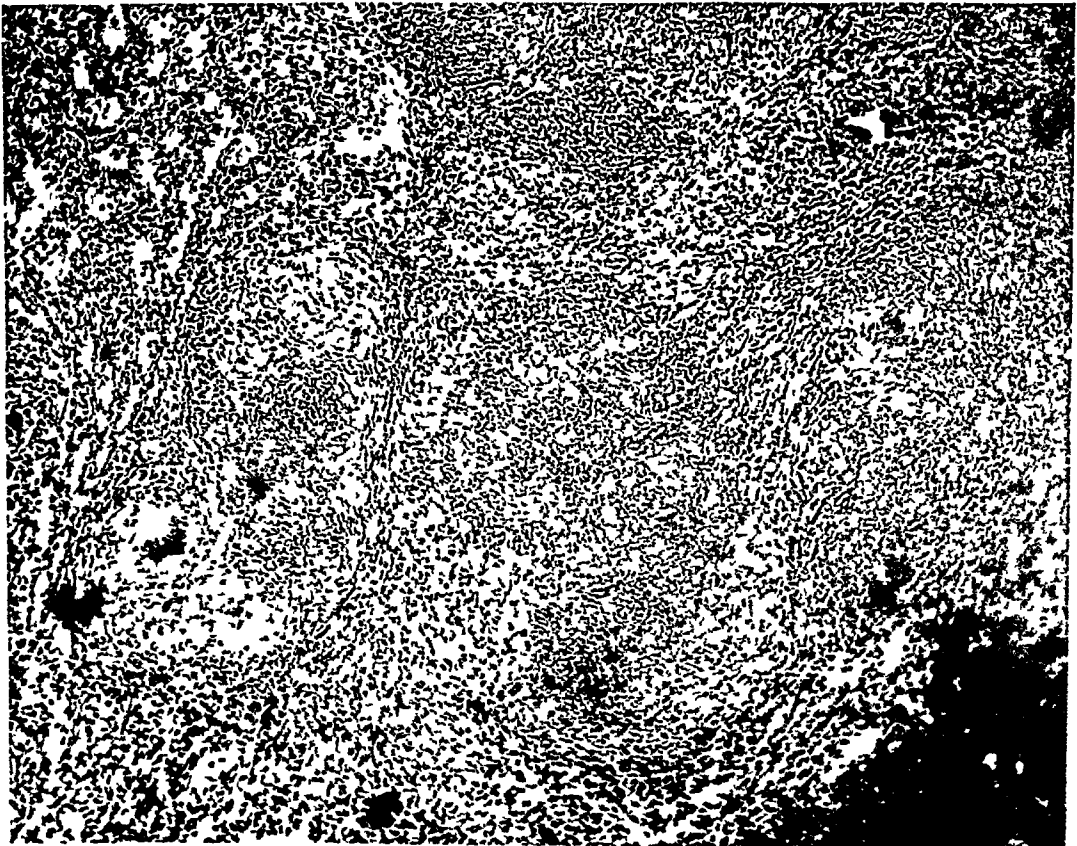


FIG 2 Photomicrograph of Figure 1, showing giant cells and extensive caseation necrosis

3,600, PMN, 81%, L, 18, M, 1 Clotting time—4 min Blood NCN 25 mgm Blood Wassermana negative Urine negative

*Clinical Course* The patient had a daily afternoon temperature elevation of from 100° to 102°. Five days after admission she was submitted to operation (splenectomy) with a clinical diagnosis of Banti's disease. The spleen was found to be markedly enlarged, the liver slightly so. Moderate ascites was present. There was no evidence of intra-peritoneal tuberculosis.

Following the operation, the patient made an uneventful recovery, and was discharged two weeks later.

*Pathological Report* The spleen was of firm consistency, weighing 2200 grams, and measuring 25 cm in its longest diameter (Figure 5). Microscopic examination revealed a diffuse distribution of confluent tubercles. The tubercles in general were small, consisting of avascular epithelioid

whorls with large multinuclear giant cells. In addition there was a diffuse fibrosis of the splenic pulp with large areas of caseation due to breaking down of tuberculous masses. A few myeloid areas were distributed through the splenic pulp (Figure 6).

*Pathological Diagnosis* Chronic tuberculosis of the spleen with recent dissemination.

### DISCUSSION

An analysis of the above three cases of primary tuberculosis of the spleen from the standpoint of their clinical resemblance to Banti's disease reveals several features which are of particular significance. In the first place, the age incidence is similar in both conditions. In his discussion on Banti's disease, Osler<sup>12</sup> states that "it is a disease of young and middle life, the majority of

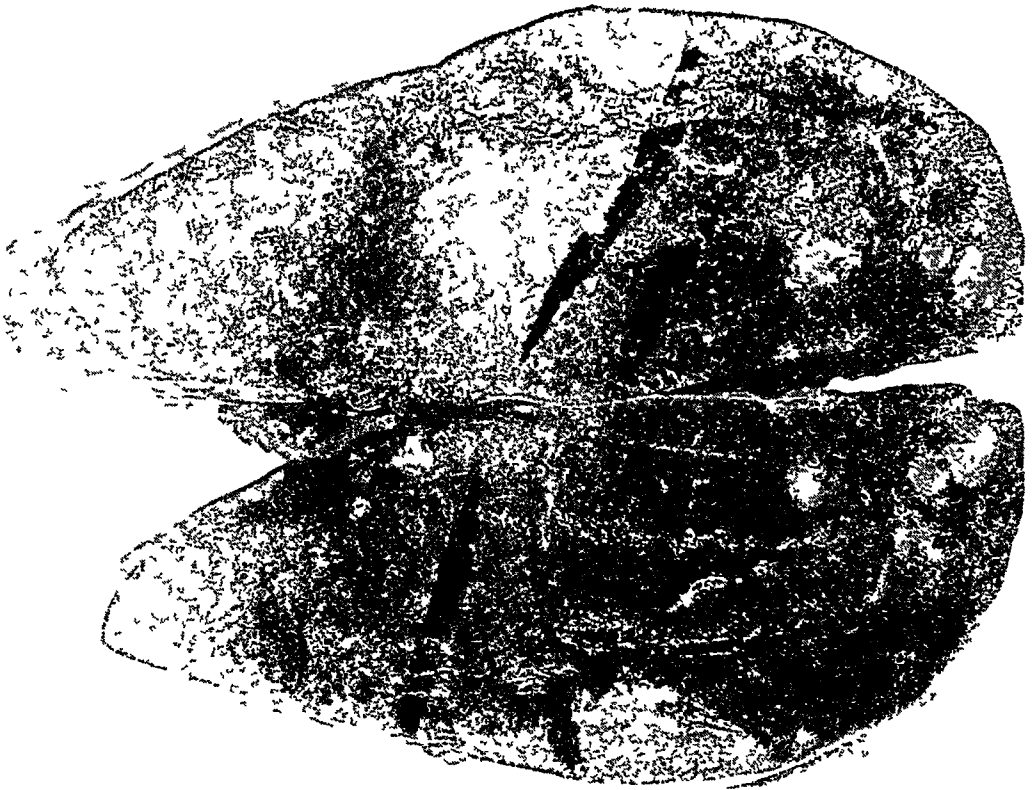


FIG 3 Cut section of spleen showing area of caseation necrosis at periphery

cases occurring before the fortieth year" In the cases reviewed by Winternitz<sup>10</sup>, fifty per cent occurred between the ages of twenty and forty In our cases, the maximum age was forty-one A second feature of even greater significance is the associated splenomegaly and liver enlargement While a well established combination in most cases of Banti's disease, its occurrence in tuberculosis of the spleen is probably less frequent In the literature one finds reference made to this in various case reports, notably those of Drebeschok<sup>13</sup> and also of Palumbo<sup>14</sup> Indeed, the latter would consider tuberculosis of the spleen with associated liver enlargement as a distinct group The de-

gree of splenomegaly has varied considerably—the spleen in Giffin's<sup>1</sup> case weighing more than five hundred grams (508 gm) while in Halleimann's<sup>15</sup> case it exceeded two kilograms (2850 gm) The hepatic enlargement has been equally variable Pathologically, while some similarity to Banti's disease was noted in one case (Tapie<sup>16</sup>) the morbid anatomy in splenic tuberculosis has been of several types Thus a miliary form has been described by Bufalini<sup>11</sup> and more recently by Moses<sup>17</sup> Tuberculous cysts of the spleen have been reported by Hayden<sup>18</sup>, and also by Peck<sup>19</sup>, while a third type was described by Ceyon, Clog and Biun<sup>20</sup> in which large areas of necrosis were scattered



FIG 4 Photomicrograph of Figure 3, showing tubercles with giant cells and adjacent epithelioid zone

throughout the splenic tissue. The first and to a lesser extent the second of our three cases belong to the latter class.

Ascites, often seen in cases of Banti's disease in the terminal stages, has also been noted in tuberculosis of the spleen. In the case described by Palumbo<sup>14</sup>, the ascites was associated with a "chylothorax". In our series, free peritoneal fluid was present in two cases (Cases 1 and 3).

The blood picture has been of interest because of its diverse manifestations. Winternitz<sup>10</sup> found a normal blood count in thirty-four, an anemia in forty-two and polycythemia in twenty-three per cent of cases. Other cases showing a polycythemia have been reported by Rendu and Widal<sup>21</sup>, Cöyon, Clog and Brun<sup>20</sup>, and also by

Head<sup>22</sup>. An anemia with an associated leukopenia, not unlike that frequently seen in Banti's disease, has been noted by Drebeschok<sup>13</sup>, Giffin<sup>1</sup> and Hallermann<sup>16</sup>. Cases 1 and 2 in our series belong to this group. On the other hand, the relative polynucleosis in the first and third of our cases stands in contrast to the lymphocytosis usually seen in Banti's disease. Still another type is found in those cases having a leukemic blood picture. Hallermann<sup>16</sup>, in 1927, reported a case having a preoperative diagnosis of aleukemic leukemia, with a total white count of 4,300 and eighty-three per cent lymphocytes. Giffin<sup>1</sup>, several years earlier, reported a case of miliary tuberculosis of the spleen having a blood picture which was typical of myelogenous

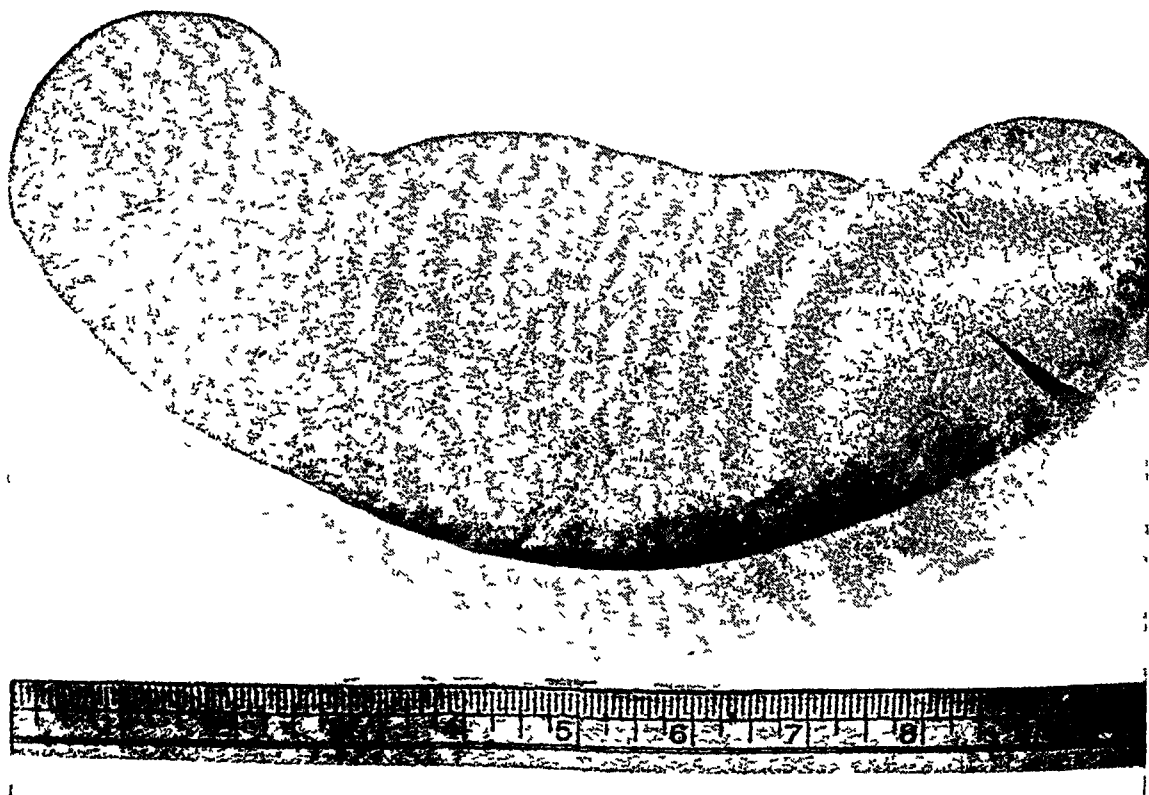


FIG 5 Longitudinal section of spleen

leukemia, and a second one having the characteristics of an aplastic anemia. It is interesting to note in this connection that Case 1 in this paper was originally diagnosed "myelogenous leukemia" because of the large number of myelocytes in the blood stream.

There is no characteristic symptomatology which would aid one in distinguishing primary tuberculosis of the spleen from other types of splenomegaly. The upper left quadrant tumor with the accompanying weakness, pain and resulting pressure symptoms might be found in almost any splenic disease, and although several diagnostic procedures have been suggested by different writers, viz, tuber-

culin reaction (Bayer<sup>3</sup>, Bufalini<sup>11</sup>) splenic puncture, etc., it is only by microscopic study of the splenic tissue after laparotomy, that the diagnosis can be established with certainty. Special mention, however, should be made of fever as a diagnostic criterion, because on several occasions this has been offered as the differentiating factor. While one finds it recorded in many cases of splenic tuberculosis, it is only rarely seen in Banti's disease. An afebrile course, on the other hand, should not rule out the former. Thus Bayer<sup>3</sup> states that it may exist with or without fever, while Magnac<sup>23</sup> reports a case with a normal temperature. In the series reviewed by Winternitz<sup>10</sup>,

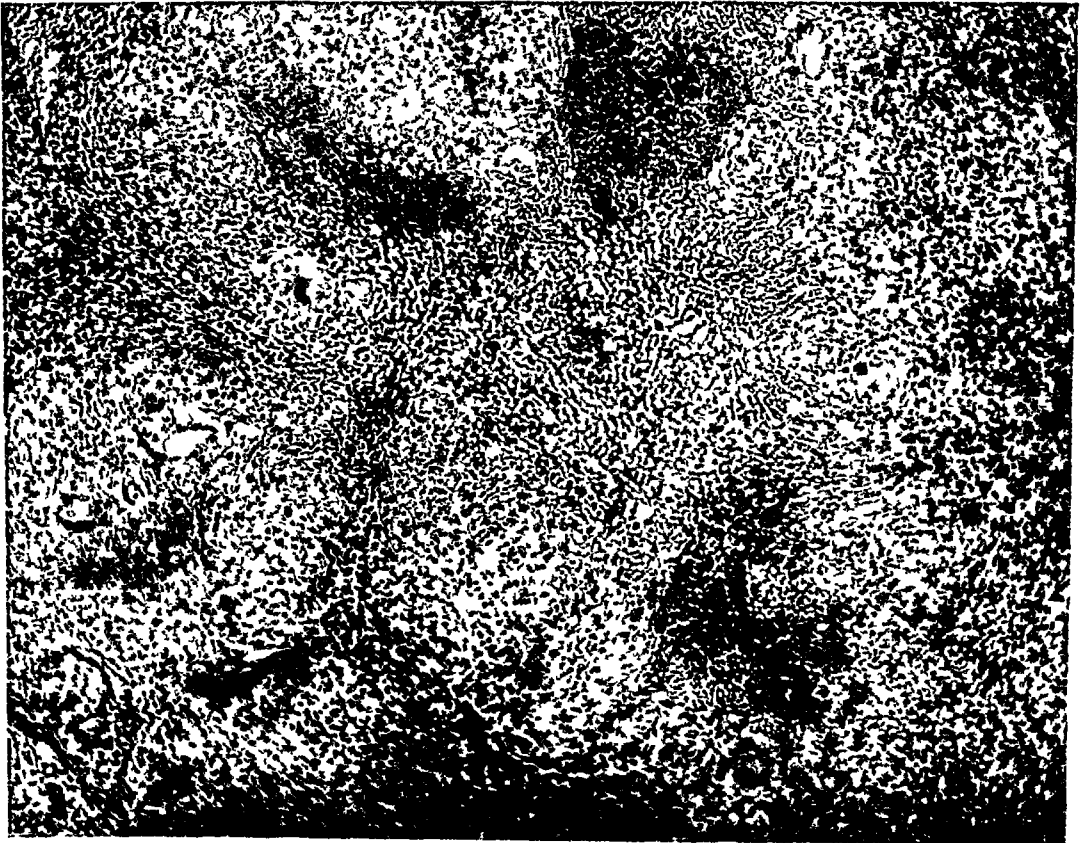


FIG 6 Photomicrograph of Figure 5, showing diffuse fibrosis of splenic pulp and many giant cells

twenty-one percent had normal temperatures. Some degree of fever was present in all of our cases.

The treatment of tuberculosis of the spleen, like that of Banti's disease, is surgical—i.e. splenectomy. This has been discussed quite at length by Linder<sup>24</sup>, Delore<sup>25</sup>, Villard and Santay<sup>26</sup>, Carling and Hicks<sup>27</sup>, and others. Fiaske<sup>28</sup> reports the results of splenectomy in ten cases which were operated upon from a series of twenty-nine. Seven recovered. Roentgenotherapy has also been advocated. In the report by Hallermann<sup>15</sup>, X-Ray was used with apparent success for four years, but at the end of that time the original symptomatology returned.

A review of the literature reveals comparatively few instances in which the clinical similarity between tuberculosis of the spleen and Banti's disease is discussed. Thus in 1927, Sartorari<sup>29</sup> described the case of a man, 46 years of age, whose symptomatology consisted of general debility, pain in the left upper quadrant, fever and night sweats. Physical examination showed the patient to be anemic with an enormous enlargement of the spleen and a moderately enlarged liver. Lungs and sputum were negative. The blood picture showed a secondary anemia, with a white count of 4,000 and the following differential: P, 63%, L, 21%, M, 17%. A subsequent blood count made ten days later showed a

definite lymphocytosis of 71%. A pre-operative diagnosis of Banti's disease was made and splenectomy performed. Five days after operation, the patient died, the spleen showing diffusely disseminated tubercles with some caseation. The liver also showed numerous tubercles. A second case which came to operation with a preoperative diagnosis of "Banti's disease" was reported by Bufalini<sup>11</sup>.

### SUMMARY AND CONCLUSIONS

Three cases of primary tuberculosis of the spleen are reported and one case from the literature is reviewed. In all four, a close similarity to Banti's disease was noted. The resemblance between the two conditions was based not only upon the general symptomatology, such as pain and tumor in the upper left quadrant, weakness, etc., but also upon definite physical and laboratory findings, viz.—an associated liver enlargement, ascites and blood picture.

Special attention is called to the fact that fever, while usually present in tuberculosis of the spleen, is not an invariable accompaniment, and hence its absence should not rule out this condition.

The pathology of splenic tuberculosis is discussed and its variability noted.

The treatment, by almost unanimous agreement, is surgical, i.e., splenectomy.

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# Superior Longitudinal Sinus Thrombosis With Subarachnoid Hemorrhage

## Report of a Case\*

By ROY S LEADINGHAM, M D, F A C P, *Atlanta, Ga*

**S**UBARACHNOID hemorrhage may be the primary cause of death following injury to the head, or may result from a variety of intracranial vascular lesions. Smith<sup>1</sup> lists as the most common causes, aside from trauma cerebral aneurysm, toxic infectious diseases, cerebral neoplasms, and hemorrhagic diseases. Neal<sup>2</sup>, reviewing thirty-five cases, gives the following causes —

- Head Injury 1
- Syphilis 1
- Hypertension (190 systolic) 1
- Epidemic Meningitis 4
- Pneumonia 1
- Nephritis 1
- Hydrocephalus and Mitral Regurgitation 1
- Mitral Lesion and Streptococcus Septicemia 2
- Undetermined 22

Most of these cases were children or young adults, and he suggests the possibility of accounting for many of them on the basis of an inherent weakness of the blood vessels. In support of his suggestion, he cites the fact that others have interpreted increased bleeding and coagulation times as evidences

of certain hemorrhagic diatheses, and refers to Meylahn's conclusion that spontaneous meningeal hemorrhage nearly always occurs as a diapedesis.

Cobb and Hubbard<sup>3</sup> report five cases coming to autopsy with hemorrhages into the parenchyma of the brain as the result of venous stasis. Three were associated with sinus thrombosis and two resulted from asphyxia. In one, thrombosis occurred in the course of an otitis media and meningitis, another followed an inflammation of the pericardium, and the third was associated with extensive phlebitis in the legs and abdomen following an attack of broncho-pneumonia. All showed at autopsy congested blood vessels and diffuse areas of extravasation into the brain parenchyma, and in one there was extensive subarachnoid hemorrhage. In the cases of asphyxia, without blocking of the vessels, they concluded that hemorrhage resulted from cerebral anoxemia.

### SYMPTOMS

While most hemorrhages occur as the result of head injuries, the symptoms of those appearing as sequelae or complications in other conditions may be misinterpreted. Meningeal irrita-

\*From the Pathological Laboratory of the Grady Memorial Hospital

tion, choked disks, leucocytosis, and evenly distributed red blood cells in the spinal fluid constitute a diagnostic syndrome in most instances, but associated with moderate elevation of temperature, headache, vomiting, stiff neck, early motor changes, positive Kernig's and Brudzinski's signs, the symptoms may be mistaken for the early manifestations of meningitis

Doyle<sup>4</sup> reports four cases of thrombosis of the superior longitudinal sinus discovered at autopsy but not diagnosed during life. He concludes that the "number, variety, and possible combination of symptoms depend on the type, size, and site of thrombus, the peculiarities of anastomosis of the cerebral veins, and ability of the cardio-

vascular apparatus to establish competent collateral circulation"

In one instance the ante mortem diagnosis was softening of the brain of infectious character, in another, abscess, in a third cerebral hemorrhage, and in the fourth, tumor

The first two followed operations for infections of sinus and mastoid. The third patient was a male, 28 years of age, with an adenoma of the thyroid gland, a basal metabolic rate of plus 27, and a blood pressure of 140/90. Twenty-four hours after admission, he had a severe headache and three days later convulsions of left foot, leg and thigh, and left upper extremities. On the fifth day he became cyanotic, stupid, and developed a left sided

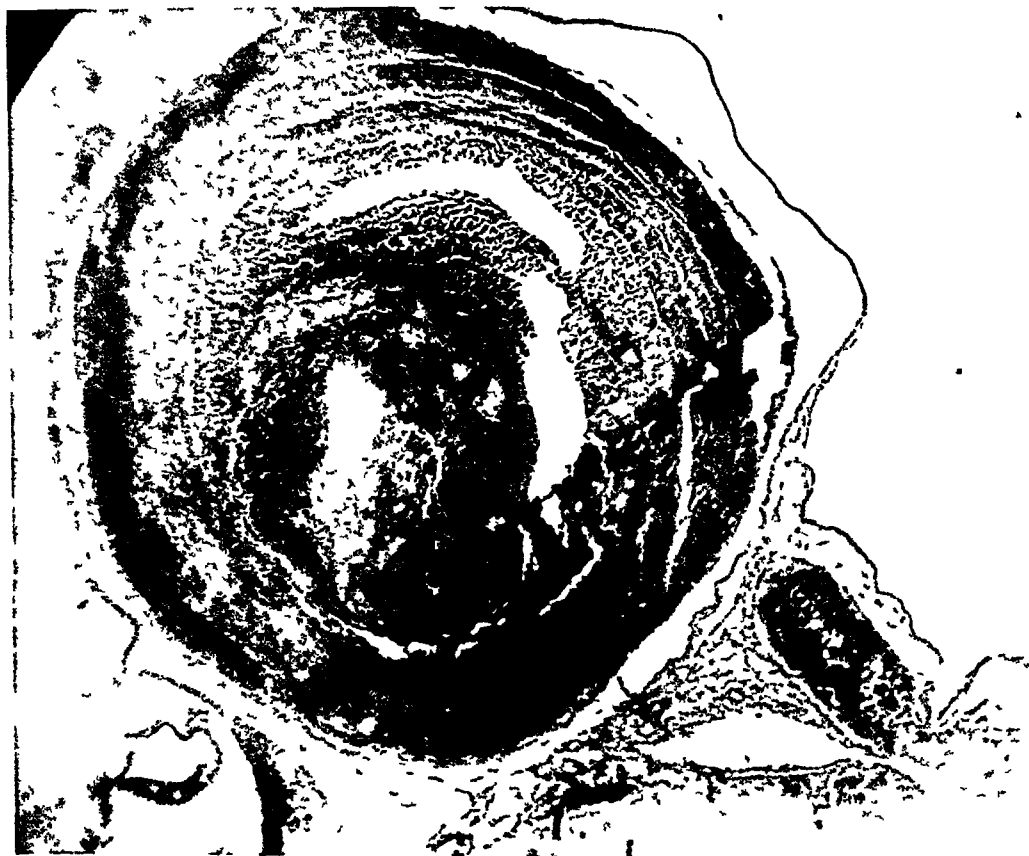


FIG 1 Thrombosis of a superior cerebral vein

hemiplegia and left homonymous hemianopsia. His spinal fluid was at first negative and later yellow tinged with pressures of 12 and 10 mm. On the seventh day he became comatose and died.

At autopsy there was thrombosis of the longitudinal sinus from the superior frontal gyrus to torcular Herophili with hemorrhagic softening of the right side of the brain from frontal gyrus to the calcarine fissure and of the left side in the region of the precentral and post-central gyri.

The fourth case was a female, age 21, who six months before admission had recurring sudden right occipitocervical headaches associated with vertigo and vomiting. Three weeks be-

fore examination the syndrome recurred with stupor and incontinence. At the time of examination there was choking of both disks, swelling of face and eyelids, paresis of conjugate ocular movements upward and laterally, cervical rigidity, and slight incoordination of right extremities. For six months she had recurring attacks of headaches, vertigo, and vomiting. On reexamination, the left patellar and Achilles reflexes were exaggerated. Lumbar puncture was negative. She died, and at autopsy, thrombosis of the superior longitudinal sinus extending into both lateral sinuses was found.

#### PATHOLOGY

Regardless of etiology or manner of occurrence, subarachnoid hemorrhage

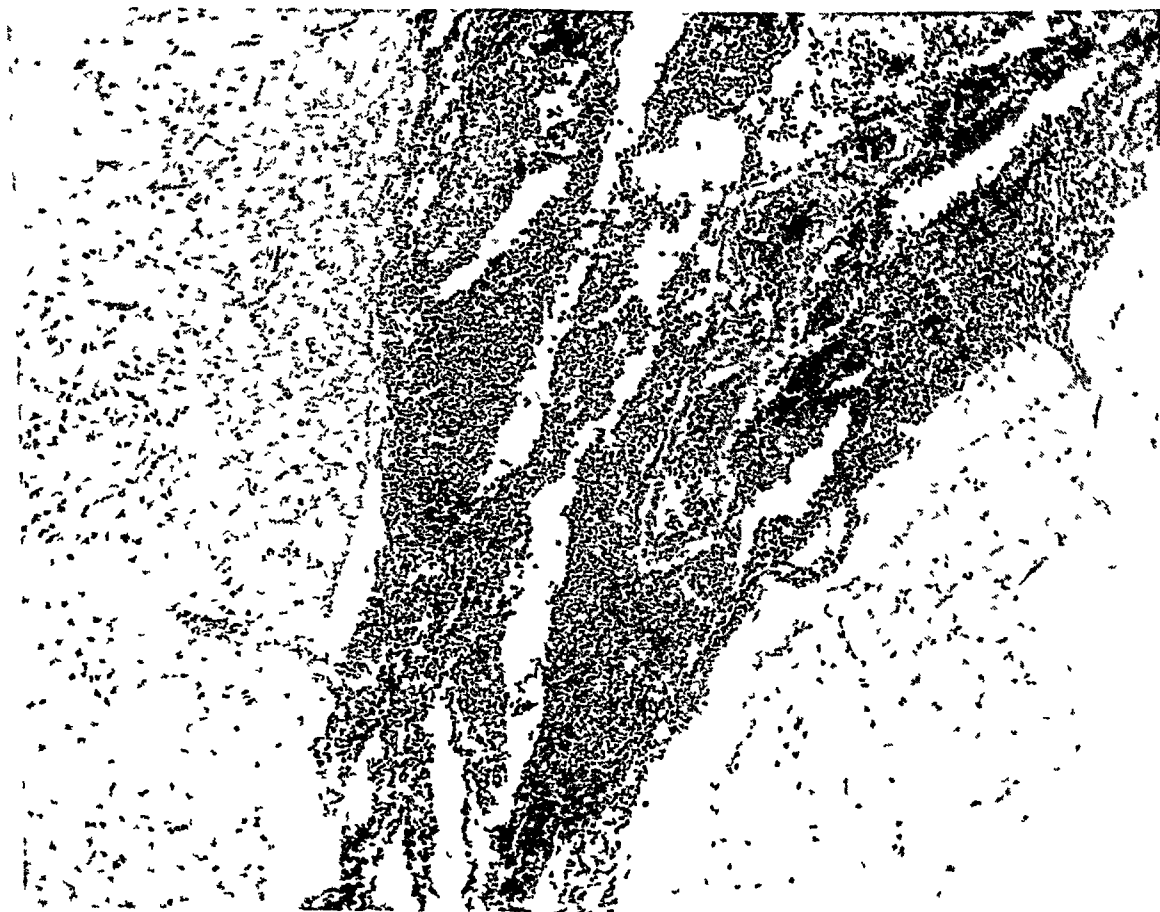


FIG 2 Diffuse hemorrhage into subarachnoid space

is commonly found at autopsy without gross lesions to designate the vessels concerned. Most of the blood is usually found about the base of the brain, and the third and fourth ventricle may contain clots.

The superior longitudinal sinus receives the superior cerebral vessels, veins from the diploe, dura, and pericranium, and at its origin, through the foramen cecum, it usually communicates with the veins of the nasal fossae.

Embolism and thrombosis may result, therefore, from widely separated focal lesions, and the resulting venous stasis within the pial vessels may easily

account for diapedesis of erythrocytes, especially in the presence of hypertension.

#### *Case Report*

A housewife, 36 years of age and nine months pregnant, entered the hospital Feb 18th, complaining of occipital headache, swollen feet and ankles. Her blood pressure was 200/138, and her urine contained from a trace to three plus albumen without red blood cells, casts, or pus. There were 22 mgs of non-protein nitrogen, 2 mgs of urea nitrogen, 90 mgs of sugar, and 1 mg of creatinin in 100 cc of blood. The phenol-sulphonphthalein output was 70% in two hours. Mosenthal test showed a range of specific gravity from 1.000 to 1.012, and a total urinary output of 1125 cc in twenty-four hours. Her blood Wassermann was negative, and blood count 5,730,000 red blood cells and 11,800 leucocytes with 52% neu-

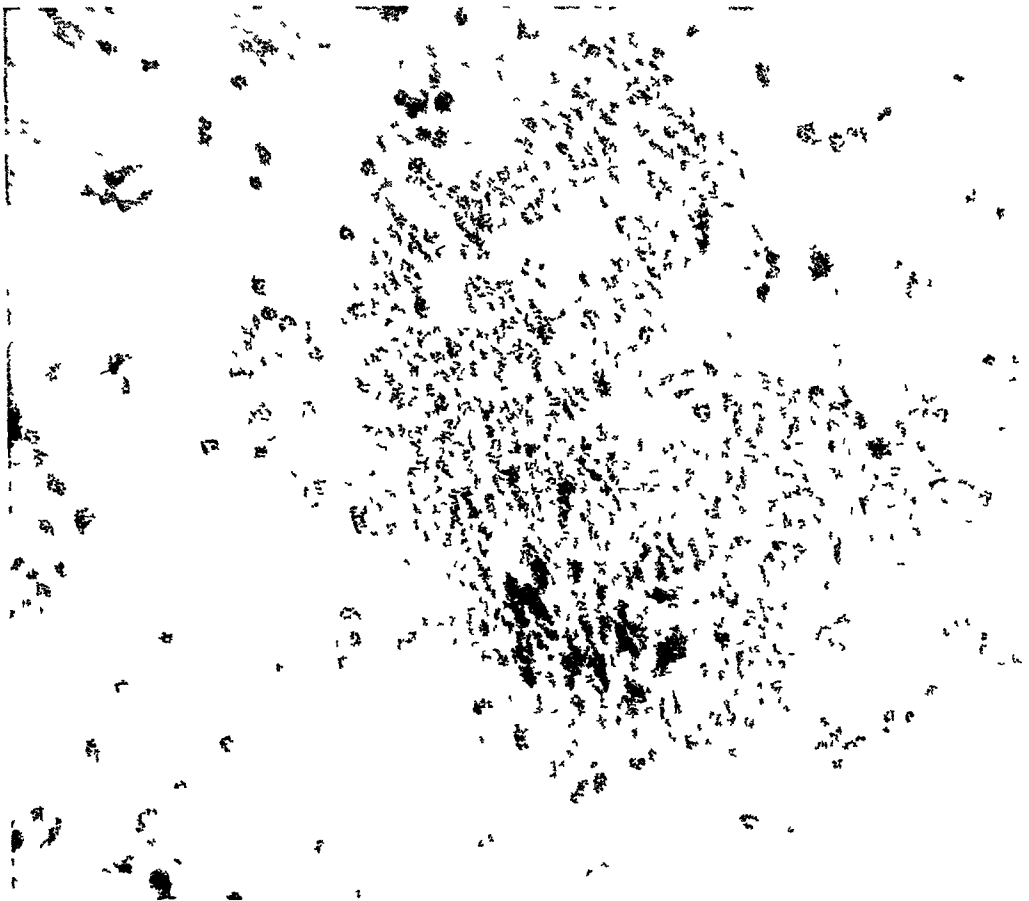


FIG 3 Area of hemorrhage and degeneration in cortical parenchyma

trophils. Aside from three pregnancies, complicated by ante partum eclamptic attacks, her past history was negative.

On admission her temperature was 98.3 F, pulse, 70, and respirations, 18. There was no cardiac enlargement, and the only abnormalities other than edema of the lower extremities were carious teeth and diseased gums. Ten days after admission she gave birth to a girl baby weighing four pounds and fifteen ounces. A week later she was sent home in relatively good condition. Her blood pressure at the time of dismissal was 140/110. Two days later, on March 9th, without apparent cause, she had a convulsion and the next day was returned to the hospital. She was received in a semicomatose condition, and from eleven forty-five to five fifty P. M. had ten generalized convulsive seizures lasting one half to two minutes each. Her blood pressure was 150/90, temperature 102° R, pulse, 120, and respirations, 30. During the next five days she gradually regained consciousness, but on the 12th her gaze became fixed and she had a short clonic convulsion of both lower extremities. Her blood pressure was 160/108. On the 14th her neck became stiff, Kernig's sign was positive, and there was bilateral papilledema. The spinal fluid was blood tinged and contained five leucocytes per cubic millimeter of fluid. Wassermann and colloidal gold tests were negative, and no bacteria were found on culture. 15 to 25 cc of blood tinged spinal fluid were removed daily on the 14th, 15th, 16th, 17th, and 22nd.

On the 16th, she began to cough and complain of pain in the lower left side of the chest. There then followed limited expansion, distant breath sounds, and, on percussion, dullness from the angle of the left scapula downward. The leucocyte count increased to 18,600 with 91% neutrophils. On the 23rd, she became restless and talked at random. Her temperature reached 103° R, pulse, 144, and respirations, 44. She developed a right sided hemiplegia and died on the afternoon of the 24th, fifteen days after admission.

An autopsy was performed an hour after death. There was an abscess the size of a hen's egg at the posterior inferior border of the lower left lobe of the lung, and scattered areas of broncho-pneumonia and edema in

both lower lobes. There was no growth of bacteria after 72 hours of incubation of the heart's blood in dextrose bouillon.

All cortical blood vessels of the brain were congested. The superior longitudinal sinus was filled with an organized thrombus which extended into the superior cerebral veins of both hemispheres. There were large areas of subarachnoid hemorrhage, especially over the left parietal and occipital lobes and over the right parietal lobe in the region of the longitudinal sinus. Cut surfaces showed no gross hemorrhage within the brain parenchyma. On microscopical examination, however, all blood vessels were engorged, and in the cortical substance of the brain, there were scattered large and small areas of edema and softening, with rare foci of extravasated red blood cells. About the thrombosed vessels of the pia there were larger extravasations into the subarachnoid space.

Other organs showed no gross or microscopical pathological processes.

#### SUMMARY

The above pathological syndrome is recorded as an instance of subarachnoid hemorrhage resulting from sinus thrombosis and venous stasis.

Considering the subsequent pulmonary lesions, it might be suggested that thrombosis of the sinus originated as a phlebitis of the veins of the nasal fossae accompanying an upper respiratory infection. Arterial hypertension should have contributed to the diapedesis of red blood cells from the congested pial vessels.

<sup>1</sup>SMITH, WM. A. Spontaneous Subarachnoid Hemorrhage, *So. Med. Jour.* 1930, 23:494.

<sup>2</sup>NEAL, J. B. Spontaneous Meningeal Hemorrhage, *Jour. Amer. Med. Assn.* 1926, 86:6.

<sup>3</sup>COBB, STANLEY, and HUBBARD, JNO. J. Cerebral Hemorrhage from Venous and Capillary Stasis, *Am. J. Med. Sc.* 1929, 178:693.

<sup>4</sup>DOYLE, JNO. B. Obstruction of the Longitudinal Sinus, *Arch. Neur. and Psych.* 1927, 18:374.

# Gland Extracts in Experimental Carcinoma and Sarcoma of Albino Rats

By O M GRUHZIT, M D, *Research and Biological Laboratories, Parke, Davis and Company, Detroit, Michigan*

RECENT publications directed to the possible beneficial effect of organ extracts in cancer, have led us to evaluate a number of these extracts in experimental carcinoma and sarcoma of rats

## EXPERIMENTAL

A series of albino rats were inoculated with the Flexner-Jobling carcinoma\* or Jensen sarcoma\* of rats. When the tumor reached in size about one square centimeter the animals were divided into three groups and placed under treatment. One group was treated with the hormone extract, the second group remained as untreated controls and the third group was placed on treatment with an extract of oxen testis prepared in a similar manner as the hormone extract. The group of tumor rats treated with the oxen testis extract served as a control for a non-specific protein effect.

The extracts were administered subcutaneously on the opposite side from the growing tumor. Six daily injections per week were given in maximum tolerated doses. On the death of the animals a careful necropsy was performed. Absence of plainly visible neoplastic tissues in the tumor was fol-

lowed with a microscopic examination of fixed tissues for neoplastic cells.

The suprarenal cortex extracts were prepared either in accordance with a recent patented process\*\* or as described below. Since the above patented extract is of unspecified concentration, we adjusted it so that one cc contained extractive material from one gram of fresh sheep cortex substance. In this concentration the extract contained traces of adrenalin. For convenience this extract is designated as cortex extract E.

For a comparative study, a suprarenal cortex extract from fresh beef suprarenal cortex material was prepared by mixing it with 16 volumes of 0.17 per cent hydrochloric acid and allowing it to stand for 45 minutes at room temperature. The mixture was then continuously stirred and gradually brought to 96° C. The mixture was then filtered through soft filter paper by gravity. The reaction was adjusted to pH 4.65. The clear filtrate was chilled overnight in the refrigerator.

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\*Original tumor bearing rats were obtained from Dr. F. C. Wood and the U. S. National Institute of Health.

\*\*U. S. Patent 1771976 granted to Coffey and Humber on July 29, 1930.

and filtered through a Mandler filter. One cc of the extract represented extractive material of one gram of fresh gland cortex substance. The adrenalin content was equal to 1:2000. This extract for convenience was called cortex extract A.

A portion of the above extract was saturated with sodium chloride and filtered. The filtrate was discarded. The residue was dissolved in acidulated water so that one cc corresponded to one gram of fresh cortical material. The reaction was adjusted to pH 4.65. The solution was chilled and filtered through a Mandler. The adrenalin content was equal to 1:40,000. This extract is referred to as cortex extract B and is practically free from adrenalin.

The thymus extract was prepared according to published directions<sup>2</sup> and contained per cc extractive substances equivalent to 0.6 grams of fresh glandular tissue.

The oxen testis extract C was prepared in accordance with the process used for cortex extract E, but was adjusted so that one cc represented extractive substance from 0.5 gm of fresh testis gland. The testis extract D was prepared in a similar manner as the cortical extract A and it was adjusted so that one cc contained extractive substances from 0.5 gm of fresh testis gland.

The cortical extract A was administered at first in 0.12 cc and was increased to 0.25 cc per day for eighteen injections in twenty-one days. This treatment was followed with the extract B in 0.25 cc doses and increased to 0.5 cc per day for seventeen injections in twenty-one days. The oxen testis extract was given at first in 0.2

cc doses and later it was increased to 0.4 cc per day for thirty-six injections in forty-two days. The control carcinoma rats remained untreated.

In Figure 1 it is noted that the Flexner-Jobling carcinoma growth in rats of series I under treatment with cortical extracts A and B of high and low adrenalin content respectively, at no time showed regression in the size of the tumor during a period of forty-two days with thirty-six injections.

The Flexner-Jobling carcinoma in albino rats treated with the oxen testis extract D of 0.2 to 0.4 cc per day with a total of thirty-six injections in forty-two days at the end of forty-nine days had caused no regression of the tumor growth. The growth of the tumor materially did not differ from that of the control or from the animals treated with cortical extract of high or low adrenalin content.

The tumor growth in the control animals in this series behaved similarly to the treated rats. The greater size of tumors in this control group after the first twenty days is accounted for by the death of a few animals with smaller tumors, thus considerably increasing the average tumor size of the remaining animals. In none of these Flexner-Jobling carcinoma tumor bearing rats did the tumor growth regress and disappear.

Another group of rats of series 2 similarly inoculated with Flexner-Jobling carcinoma, but containing twenty to twenty-nine tumor bearing animals in each of the three groups, besides a group of rats of series 3 with tumors ulcerated and far advanced, were placed on suprarenal cortex extract E. This extract was administered

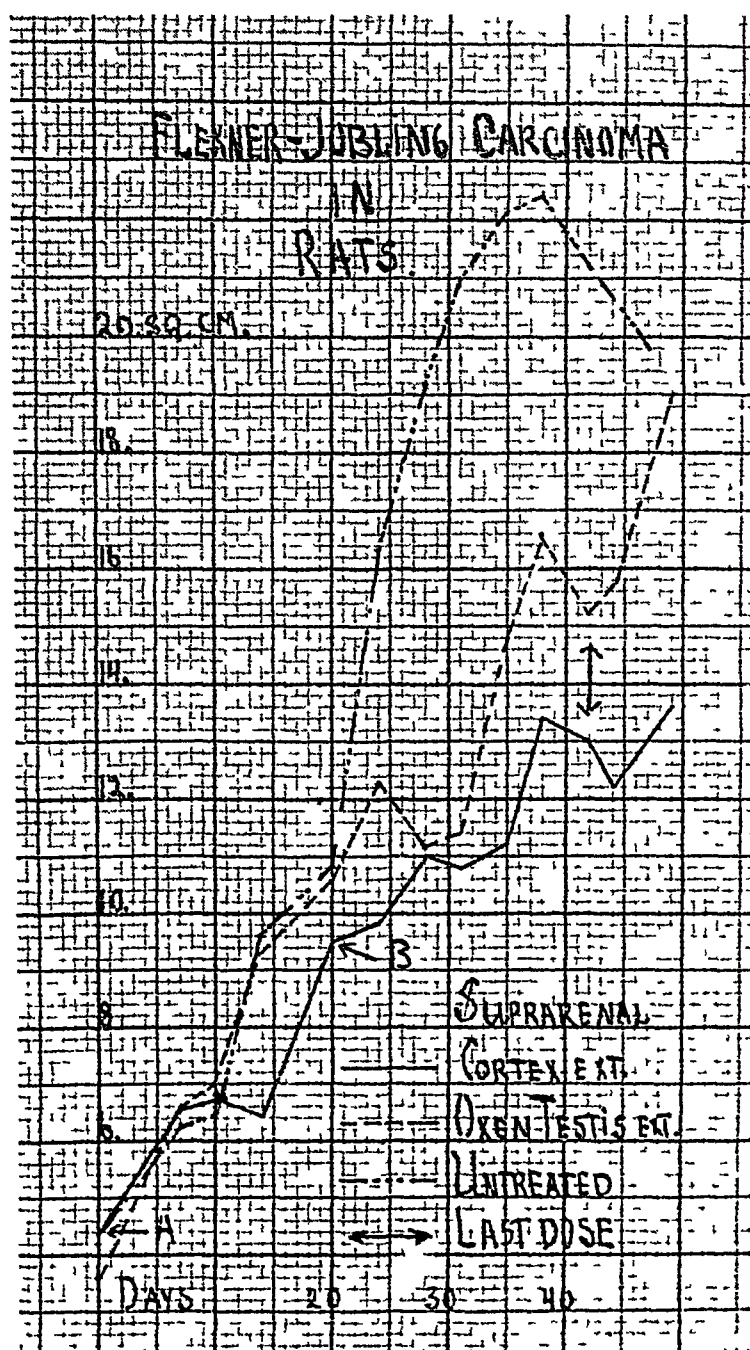


FIG 1 The Rate of Growth of Flexner-Jobling Carcinoma in Albino Rats Under Treatment with Suprarenal Cortex and Oxen Testis Extracts as Compared with Untreated Tumor Bearing Rats



beginning with 0.0625 cc per day and increasing rapidly to 0.15 cc in six days for twelve injections and then the dose was increased to 0.2 cc daily and carried until the end of the experiment of nine weeks.

A similar group of twenty-eight tumor bearing rats was placed on treatment with oxen testis extract C prepared in a similar manner to the cortex extract E. This extract was given to rats in 0.2 cc daily. The third group of twenty carcinoma bearing rats remained untreated.

the beginning of the seventh week of the treatment without a regression in tumor or a disappearance of neoplastic tissues.

The carcinoma growing tumors in rats treated with 0.5 cc thymus extract (2) per day, behaved in all essential respects similarly to the ones treated with the suprarenal cortex, oxen testis or to untreated controls, as noted in Figure 2, although with a less rapid rate of growth. The examination of the tumor masses of the thymus treated animals at no time indicated a dis-

TABLE I THE AVERAGE RATE OF GROWTH OF CARCINOMA TUMOR PER RAT UNDER TREATMENT WITH SUPRARENAL AND OXEN TESTIS EXTRACTS AS COMPARED WITH NON-TREATED CONTROLS

		Weeks After Treatment									
		Before Treatment	1st Wk	2nd Wk	3rd Wk	4th Wk	5th Wk	6th Wk	7th Wk	8th Wk	9th Wk
Series 2											
Cortex Ext E	29	3.5	6.1	7.6	10.3	14.3	15.1	17.3	19.2	18.9	20.7
Oxen Testis C	28	3.1	4.1	5.4	8.1	11.9	13.8	13.3	18.0	14.0	13.0
Untreated	20	2.8	4.0	5.3	7.9	10.5	14.1	15.2	16.2	18.6	17.2
Series 3											
Cortex Ext E	7	6.51	8.44	9.74	13.6	12.92	16.92	18.95	-	-	-
Untreated	6	6.49	9.51	15.70	18.42	22.30	26.35	26.51	-	-	-

It is evident from Table I that during the nine weeks of treatment with the suprarenal cortex extract E and testis extract C, neither of the glandular extracts had a retarding effect on the Flexner-Jobling carcinoma tumor growth, and if anything, the rate of growth of the tumor in rats treated with the suprarenal cortex extract E was more rapid in comparison with the oxen testis extract treated carcinoma tumor bearing rats. The treatment with the cortical extract E in rats in which the tumor was ulcerated and far advanced was similarly ineffective as shown under series 3. The treated and the untreated rats of this series died at

appearance of the neoplastic tissues. The treatment neither delayed the tumor growth nor did it cause its regression. All tumor bearing animals, treated or untreated, died.

Simultaneously with the study of the effect of the different gland extracts on Flexner-Jobling carcinoma in rats, these extracts were used in the treatment of Jensen sarcoma tumors in albino rats. The effect of the extracts in sarcoma bearing rats is illustrated in Figures 3 and 4. The suprarenal cortex extract A with a high adrenalin content, 1:2000, extract B with a low adrenalin content, 1:40,000, and pure adrenalin in dilution of 1:1000, were

given daily in doses of 125 cc to 0.5 cc respectively for 16 to 25 days

From Figure 3 it is evident that neither of the suprarenal cortex extracts possessed more action than adienalin alone, nor that the effect of these extracts differed from that of

testis extract or untreated controls. The greater effect of adrenalin, 1:1000, on the sarcoma tumors was only casual and could not be duplicated in other experiments.

The non-effectiveness of the various organic extracts in sarcoma of rats is

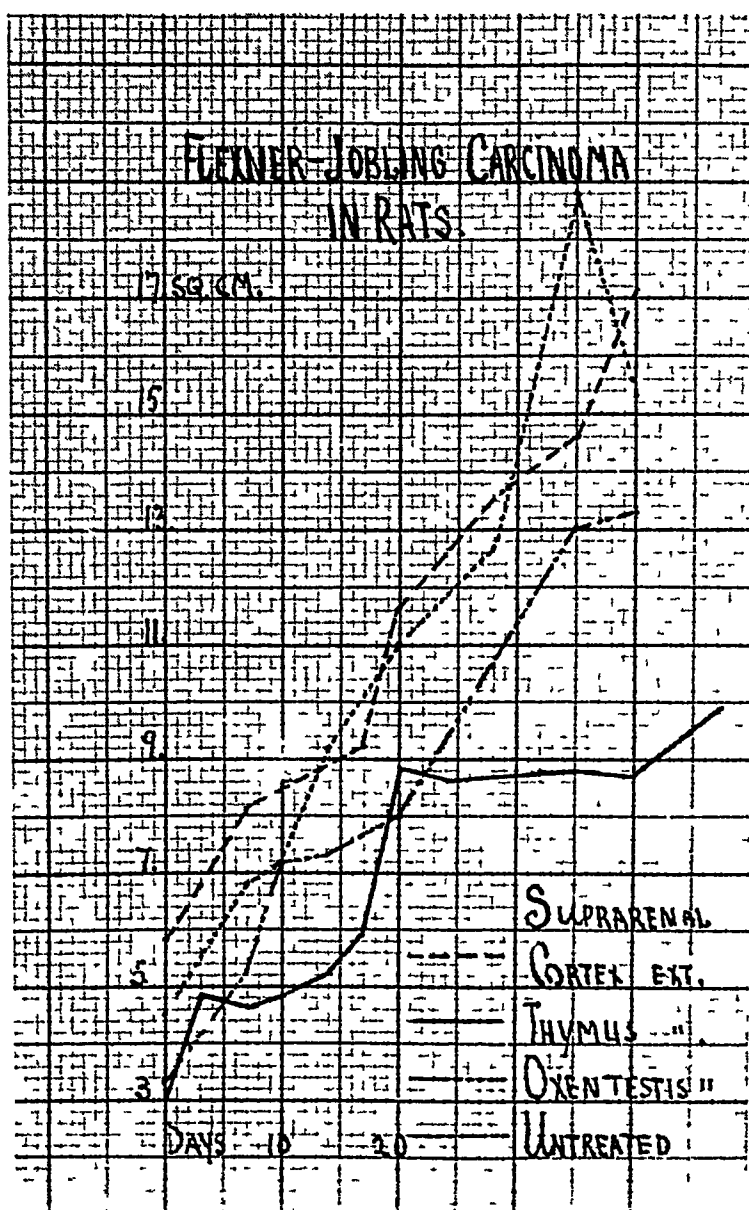


FIG. 2 The Average Rate of Growth of Flexner-Jobling Carcinoma of Rats Under Treatment with Suprarenal Cortex, Thymus and Ovary-Testis Extracts in Comparison with Untreated Tumor Bearing Rats

even more clearly brought out in the case of the thymus extract, and omentum extract, as contrasted with untreated controls (Figure 4)

The thymus extract was used in 27 rats daily for 29 days in doses of 0.25 to 0.5 cc. The rate of tumor growth and its decline is almost similar to that of the control group. The tumor reached the maximum growth irrespective of the treatment and the animals usually died from complications or absorption of the toxic necrotic material of the tumor. The death of the rats with larger tumors, leaving the smaller tumor bearing rats alive, is responsible for the abrupt decline in the curve. The untreated control tumor bearing rats show similar changes in the tumors as noted in Figure 3.

The omentum extract was made by extracting hog omentum with 80 per cent ethyl alcohol. One-half of a cc of the water-soluble part was given daily to tumor bearing rats for a period

of 22 days. The rate of tumor growth under the treatment with this lipid extract from omentum was entirely comparable with the gland extracts. The tumors neither receded nor did the neoplastic tissue disappear.

The relation of ulceration of the neoplastic tumors in rats under the treatment with the various gland extracts is alluded to by Bishoff<sup>1</sup> as a possible effectiveness of the treatment with an organic extract. In Table II the incidence of ulceration is presented for Flexner-Jobling carcinoma in albino rats.

It is noted that the incidence of ulceration is less in untreated than in treated animals. The incidence of ulceration under mineral salt administration (lactate salts of magnesium and calcium and potassium acid phosphate, one cc intravenously twice weekly of equal parts of 3, 10 and 10 per cent respectively) is considerably greater than in tumor bearing rats treated either

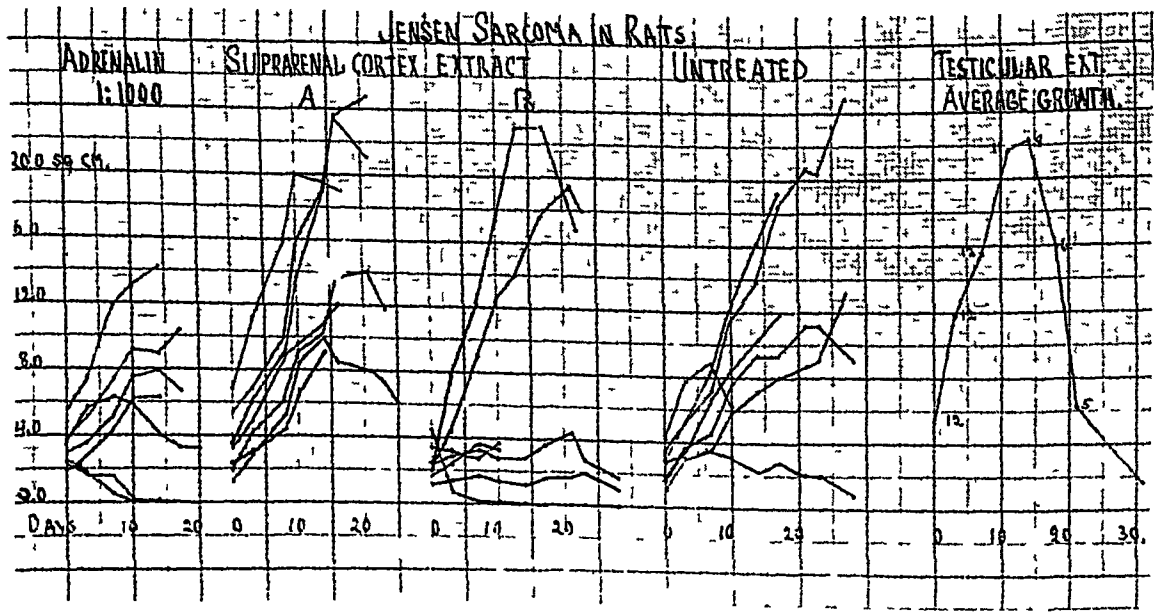


FIG. 3 The Rate of Jensen Sarcoma Tumor Growth Under Treatment with Suprarenal Cortex, Adrenalin and Oxen Testis Extracts as Compared with Untreated Controls

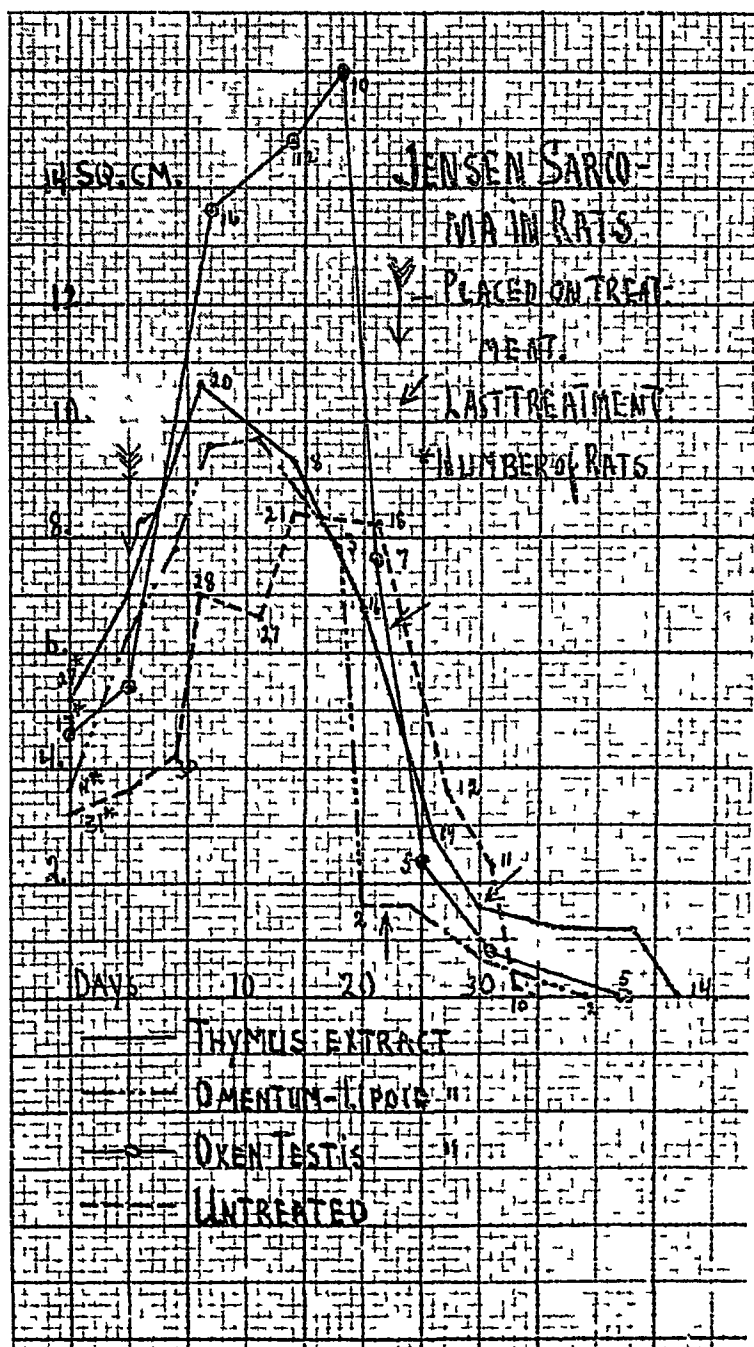


FIG 4 The Average Rate of Jensen Sarcoma Tumor Growth Under Treatment with Thymus Extract Omentum Lipoid Extract and Oxen Testis Extract as Compared with Untreated Tumor Bearing Albino Rats

TABLE II THE INCIDENCE IN PER CENT OF ULCERATION IN CARCINOMATOUS TUMORS IN RATS TREATED WITH CORTICAL, OXEN TESTIS EXTRACTS, A MIXTURE OF MAGNESIUM, POTASSIUM AND PHOSPHATE SALTS AND UNTREATED CONTROLS

		Weeks After Treatment								
Original		1st	2nd	3rd	4th	5th	6th	7th	8th	9th
No	Rats									
Series 2										
Cortex Ext E	29	10	22	33	51	65	74	87	95	95
Oxen Testis Ext C	28	8	28	28	41	67	70	70	75	77
Untreated	20	—	12 5	12 5	25	67	71	82	82	82
Series 3										
Mineral Salts	7	29	57	57*	71	86	100	—		
Untreated	6	—	—	—	—	50	65	82		

\*First week following cessation of mineral salt treatment and continued on suprarenal cortex extract E

er with oxen testis or suprarenal cortex extracts. The oxen testis extract treated rats show about the same per cent of ulceration in a given period as those treated with the cortex extract. It is apparent that none of the gland extracts caused more ulceration in carcinoma tumors in rats than could be similarly noted in animals treated with oxen testis extract or non-protein mixtures of some of the common salts of magnesium, calcium, etc.

### DISCUSSION

The Flexner-Jobling carcinoma and Jensen sarcoma growth in albino rats represents a foreign body which derives its nutrition from the circulating blood stream of the host. Any substance circulating in the blood stream *in apriori* reaches these tumor cells and exerts an action. The spontaneous tumors in animals or man are in an intimate relation with the normal structures of the host and may or may not be influenced by the substances in the blood stream. In our series of Jensen sarcoma the average spontaneous regression was about twenty-five per cent. In the case of Flexner-Jobling carcinoma the tumors regressed spon-

taneously on an average of about ten per cent. The expectancy of regressions of the foreign body type of tumors under treatment should be considerable if the treatment possessed any action. Neither Bishop and Maxwell's findings with sarcoma in rats, nor our results with carcinoma and sarcoma, suggest the slightest effect of the suprarenal cortex, thymus, omentum-lipoid or oxen testis extracts upon tumors in the tumor bearing animals.

Itami and McDonald<sup>4</sup> in a recent paper, could not demonstrate a beneficial effect of true suprarenal cortex hormone of Swingle and Pfiffner in spontaneous breast carcinoma in mice.

### SUMMARY

1 Albino rats inoculated with Flexner-Jobling carcinoma, when treated with different suprarenal cortex substance extracts both with high and low adrenalin content, showed neither a delay in the growth of the tumors or their regression as compared with either untreated tumor bearing rats or those treated with a non-specific protein extract of oxen testis.

2 The treatment with thymus extract neither inhibited the growth or

caused the carcinoma tumors in rats to regress. Injection of the extract did not prolong the life of the tumor bearing animals.

3 The suprarenal cortex extracts with high or low adrenalin content, the thymus, the omentum-lipoid and the oxen testis extracts neither inhibited growth nor caused regression of the Jensen sarcoma tumors in albino rats.

4 The rate of ulceration of carcinoma tumors under treatment with various gland extracts was not greater,

as compared with the rate of ulceration of similar tumors in rats under treatment with inorganic salts or with a non-specific extract of oxen testis.

5 The organic extracts studied in experimental carcinoma and sarcoma in rats had no beneficial effect in inhibiting growth of the tumors, their regression, nor did the extracts cause prolongation of life of the tumor bearing animals, as compared with untreated tumor bearing animals or those treated with non-specific protein extracts.

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# Amebic Dysentery: Sugar Cane as a Possible Distribution Hazard\*

By MILLS STURTEVANT, M D , F A C P , *New York*

**O**CCASIONAL cases of amebic dysentery have been seen in large clinics in the United States for forty years<sup>1 2</sup> Amebic dysentery has, however, been regarded until about fifteen years ago as a tropical disease

Since 1916 epidemics, sporadic cases, carrier cases, infected individuals who have never been out of their respective localities have all been reported from France<sup>3 4</sup>, England<sup>5,6,7</sup>, Canada<sup>8</sup> and the United States<sup>9,10,11</sup> Three editorials have appeared in the Journal of the American Medical Association<sup>12 1 14</sup> calling attention to reports of the disease in twenty-four states and suggesting that cases may be expected in any locality in the United States Feder<sup>15</sup>, Musser<sup>16</sup>, Dowling<sup>17</sup>, Brown<sup>18</sup>, Kaplan, Williamson and Geiger<sup>19</sup>, Craig<sup>20</sup> and others have written of cases seen in a variety of localities

Conveyance of the cysts to man so that he swallows them and becomes infected may be by food or water It has been suggested that rats<sup>21</sup>, cats and flies<sup>22</sup> may have a part in distribution of the cysts Infected market gardeners,

food handlers and cooks have been mentioned as distribution hazards

Two cases have come to the attention of the writer where another possibility is suggested

Patient A A was admitted to Bellevue Hospital September 25th, 1927, 20 years old, a dishwasher He was a native of Salvador, Central America and had been in this country two years, all of the time in New York Thirty-three days before admission the patient began to have loose movements which increased in frequency and became bloody Three or four movements at first soon became ten to fifteen a day With this he had cramplike pain in the abdomen which also increased rapidly in severity This was relieved by bowel movement Proctoscopic examination revealed ulcers which Dr Elmer I Huppert thought were characteristic of amebic dysentery Dr Joseph Connery found and identified the *Endamoeba histolytica*

No good lead could be discovered as to the source of this infection with the following exception The patient had a friend whom he had known in Salvador and who worked on a boat plying between New York and Salvador Three days before the onset of his symptoms and thirty-six days before

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\*From the Department of Medicine, The University and Bellevue Hospital Medical College New York University and The Third Medical Division, Bellevue Hospital

admission he had visited his friend on a boat which had just come in from Central America. The friend had brought some sugar cane and our patient had enjoyed several stalks, biting into the stalk and sucking the juice. This seemed a possible manner of infection.

Patient A. C. applied for treatment October 24th, 1928. He was 30 years old and had always been well until a year before when he had contracted diarrhoea in Los Angeles. This had persisted with an average of 5 or 6 movements a day and 1 to 3 at night. The movements were bloody and accompanied by lower abdominal pain. Bowel movement relieved the pain to a great extent. Proctoscopic examination showed ulceration which suggested

amebic infection. Dr. Joseph Connery found and identified *Endamoeba histolytica*.

This patient at the time of the onset of his disease had been working on the dock in Los Angeles. He had helped unload boats from various ports and had eaten some sugar cane. He did not know that any of his fellow workmen who also ate the sugar cane contracted diarrhea.

#### CONCLUSION

Two individuals with proved amebic dysentery are cited who had eaten of sugar cane brought from the tropics. Since no other likely method of infection of these persons could be discovered it is suggested that sugar cane may carry the cysts of the *Endamoeba histolytica*.

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# Reasons for the Artist's Conception of the Physician

By BEN WOLEPOR, M D, *Philadelphia, Pa*

JOSEPH CONRAD defined the artist as one who in a moment of courage, snatched from the remorseless rush of time, a passing phase of life, one who attempted the highest kind of justice to the visible universe by bringing to light the truth. The artist appeals to that part of our being which is not dependent on wisdom, to that in us which is a gift and not an acquisition—and therefore more permanently enduring. This is an eloquent and stirring description but far from a true one. The artist cannot describe truth in its entirety. His vision is often distorted by an inner myopia. He is subject to the vicissitudes of life which temper his art. One needs but regard the works of Goldsmith and Crabbe. The former wrote a cheerful poem of a village in which youth disported on the green and enjoyed life to the full, the latter described a harrowing scene, in which ingratitude and feeble old age predominated. The villages described resembled many other English communities of the period but the different personalities of two great poets regarded the same object in a markedly different way.

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\*From the Graduate School of Medicine, University of Pennsylvania

An artist is the instrument of his age, a victim, as are all men, of its weakness and a participant in its glories. He differs in that he gives voice to the views of his contemporaries. At times he becomes prophetic and foresees the future if he possess the piercing vision of genius that annihilates the differentiation of Time, that makes the present and the future merge into one. This is indeed a rare quality. He is a favored mortal if he be only one who makes his age articulate rather than one who is the instrument of the world and of all time, then only does the artist fulfill Conrad's conception of him. Then does the poet, looking deeply within himself, see certain fundamentals which are universal and to which his gift of words gives permanence.

The artist has a difficult task. He must describe emotion, the most fluid and evanescent of all energies. He must first feel deeply so as to give his work the stamp of sincerity and then make others participate in scenes spun from the imagination. No matter how skillful he may be, he often fails to convey his complete conception of life. Anatole France has repeatedly stressed the inadequacy of words which at the best are only deficient symbols of

thought The artist's perpetual question is "How does this phase of life affect me?" and not, "What is the truth?" The truth is a matter of secondary importance to most artists. His chief task lies in interesting his reader and then, if he be fortunate, of informing him. He resorts to artifices of all types and grossly exaggerates so as to captivate the imagination. It would be futile to expect Flaubert or Swift to deal justly with the world, condemning its vices but upholding its virtues. Equanimity is the goal of the philosopher but not that of the poet.

#### THE ARTIST AS JUDGE

Despite the idiosyncrasies of the artist, his command of words gives him power which he often utilizes to attack groups of men of whom he disapproves. He is frequently correct in his appraisal of a situation but is only too often more zealous than righteous and lends verisimilitude to gross error. When he attacks Medicine he unfortunately at times finds a rich field to garner. Medicine is an honorable profession but is subject to fluctuations that occur in races, science and the Arts. In Medicine periods of decline follow those of ascent, during an interval of low ebb the vigilant eye of the critic may spy a conspicuous defect which forms the nucleus of a pitiless drama. He bases his argument upon enough truth to erect an elaborate but untrustworthy superstructure.

The tragedy of Medicine lies in its continuous dying and being reborn. In the words of Ecclesiastes "The wind goeth toward the south, and turneth about unto the north, it whirleth about continually, and the wind return-

eth again according to his circuits" Medicine makes progress and like the wind, goeth toward the south and then disaster overtakes the world, new disrupting tendencies appear that engulf all man's progress, knowledge comes to a standstill; Medicine languishes with all the other arts, and, again like the wind, turneth about unto the north and whirleth in the doldrums of universal inactivity. With a renewal of truth and light and a dispersal of ignorance, Medicine, in conjunction with the other products of man's intellect, returneth again according to his circuits.

The Medical profession had deteriorated in France in the 17th century. It was divided into three armed and battling camps, those of physicians, surgeons and barbers. They disliked and despised one another. Raynaud says that "Our fathers, absorbed as they were by learning and philosophy, by endless debates, only too often forgot that medicine is learned at the bedside. It may appear incredible, but the majority of students secured their Bachelor of Medicine degree without ever having seen a single patient. In brief, the practical side of Medicine which in our opinion supersedes everything, was then most neglected. Their desire was to shine in oratorical display. One might with truth have assumed that Medicine was only a branch of literature."

The age provided Molière with a great opportunity for the rapierlike thrusts of his wit. He thought that because doctors could not cure him and had killed his only son that they were pretentious ignoramuses, men who quoted Hippocrates and when corrected said, "Nous avons changé tout cela."

"They had," he thought, "changed everything for the worst, these rogues who wore wigs and red heels, made ostentatious use of their learning and instead of taking care of their patients, talked at great length of technical things" Molière dragged Sganarelle from the gutter, a drunkard who beat his wife and starved his children, who sold all the furniture in the house to buy liquor, and laughingly made a physician of him In a knowing way he says, "Behold a doctor who pleases me, I think he will succeed, because he is a clown"

Molière was a great dramatist but he was not impartial nor did he adhere closely to the truth He had an axe to grind He was embittered by the loss of his son, by his poor health He was also a writer of comedies who sought continuously for good material, therefore he cheerfully sacrificed the truth of the situation in order to depict the medical profession as consisting of men who when called into consultation, discuss the relative value of a mule as compared with a horse The age that Molière ridiculed was that of the great anatomists Bartholin, Riolan, Pecquet, Littre, Winslow Doctors, at the time, according to Raynaud, formed a teaching body, a lucrative and honoured profession, accessible only to the higher ranks of the middle class The welfare of one doctor had to be sacrificed to the interests of all to maintain the profession intact The Faculty of Medicine of Paris was not opposed to progress but desired that advancement in knowledge come from her and not from foreign lands She frowned upon the

view of the circulation of the blood not because it was an untenable theory but because an Englishman was the discoverer

Molière did not regard the universe as a sequence of events He described an isolated instance, the condition of Internal Medicine in France in the 17th century and condemned all doctors This was far from an historical perspective He was unaware that Sydenham was proclaiming to a rather weary world the views of Hippocrates, or that Harvey was writing his "*De Motu Cordis*", but then, rebellion was in the air Molière, like so many other great men was a product of the age and his very individualism was part and parcel of an egotistical, yearning, rebellious period Cervantes thrust Don Quixote against the antiquated windmills of tradition Bach took music and made a towering edifice of it Rembrandt merged the indignant faces of his subjects into the general scheme, Milton waged a mighty conflict in which God triumphed over a glorious though fallen angel, one who would not accept defeat but in the midst of flame and chaos hurled denunciations at his victor Strife was in the air Traditions toppled over like dead trees in a storm Freedom of thought, like a gust of wind freed man's mind from intellectual cobwebs Bruno was to die at the stake Acosta was to kill himself in defiance of a world that repudiated good motives supported by intellect because they were at variance with prevailing thought Great men may have much to do with the moulding of a period but they themselves are greatly influenced by their age One doubts

whether Shakespeare could have written his plays and sonnets in any age but the Elizabethan

#### THE ARTIST REGARDS THE DOCTOR

Disillusioned Flaubert gave scant consideration to Charles Bovary, the hardworking country practitioner and to Homais, the apothecary. He made a dupe of the former, one who lacked the vision to satisfy the romantic yearnings of an erotic wife, of the latter he made a garrulous fool. To understand an artist's conception of life one must know the artist, his relationship with life, his success or failure. Some men, like Shakespeare or Spinoza, resemble the falcon. They breast the storm, fly above the dark clouds, scream at the lightning. They will not admit defeat, but nevertheless their lives and works show the effects of the storm. They have conquered, but at a cost, and gained Heaven by way of Calvary. Flaubert was not made of Shakespearian fibre. He could write "Madame Bovary," but not "The Tempest." The odds were against him. Even as a boy he could not face failure and consequently confronted with difficulties, as one with his personality would be, became a youthful cynic. "This is a fine civilization," he cries, "an age that has invented railways and prisons, rectal pumps, cream tarts, royalty and the guillotine." He was tortured by an unceasing imagination, the curse that afflicted Madame Bovary.

The young, oversensitive Flaubert suffered at school intensely. He, like Shelley, met defeat at the hands of his schoolmates. He could not contend with a collective egotism which developed in him a deep aversion to

humanity. His ideas and unsociability were ridiculed. Tormented by his teachers, laughed at by his comrades, he sought refuge in solitude. He writes that Byron and Rabelais are the only two who have written with the intention of hurting and laughing openly at mankind. "I am incessantly dissecting, it amuses me and when I have at last laid bare corruption in something, which is thought to be fine, found gangrene in beautiful things, I lift my head and laugh. I've come to hold the firm conviction that vanity is at the base of everything." Flaubert, the analyst of human vanities, revealed at seventeen his future aesthetic formula. "I had nothing to cling to," he says, "neither society nor solitude, nor poetry nor science, nor skepticism nor religion. I was only a mummy embalmed in my own sorrow." Then he acquired epilepsy, an incurable disease. How could Flaubert write truthfully of life? He who knew life only through his own dismal sensations. Charles Bovary was a failure, Homais a fool, Madame Bovary, a disillusioned heart-broken counterpart of Flaubert who unable to stand the boredom of life, committed suicide. The story is compounded of a sequence of tragedies. It may have been truth, but only a facet of the gem called life, no more truthful in its entirety than Eugene O'Neil's "The Strange Interlude." These men and women are inhabitants of a madhouse. They crave the impossible and like spoiled children, cry because they cannot play with the moon. There is no hope for them. They are doomed from the start, for within them lies no nucleus of future battles. Defeat has stamped them in the cradle and they

bear the grisly mark to the grave Flaubert bears witness to the bias of the artist, the impinging of his personality on his work

Bernard Shaw is a vigorous antagonist of the medical profession and makes the illuminating statement that the main distinction between a quack doctor and a qualified one is the fact that only the qualified one is authorized to sign death certificates for which both sorts seem to have equal occasion. He sweeps away with a blithe hand all the drudgery which the average medical student undergoes to acquire his M.D. He gallantly darts into the turbulent sea of immunity of which he knows nothing and discusses vigorously subjects from which even an experienced metaphysician, shrinks. Shaw's conceit makes him ignore the preliminary education essential even for remote glimpses into immunity, a subject which occupies the entire attention of masters, for the theory of 1920 is only too often the fallacy of 1930. Obsessed with what he conceives to be the utter worthlessness and cruelty of animal experimentation the rock upon which physiology is based, he ascribes man's desire to learn to a specific lust for cruelty which infects even his passion of pity and makes it savage. Led by a preconception, he wages a bitter conflict with medicine, totally unaware of his bias, he utilizes his wit to lash at what he conceives to be the bane of the age the medical profession. He makes amusing but fallacious reading.

"I do not know," he writes "of a single thoughtful and well-informed person who does not feel that the tragedy of illness at present is that it

delivers you helplessly into the hands of a profession which advocates and practices the most revolting cruelties in the pursuit of knowledge. As to the honour of doctors, they have as much as any other class of men, no more and no less. And what other group of men pretend to be impartial when they have a strong pecuniary interest on one side. There is another difficulty in trusting to the honour and conscience of doctors. Doctors are just like other Englishmen, most of them have no honour and no conscience. All that can be said for medical popularity is that until there is a practicable alternative to blind trust in the doctor, the truth about the doctor is so terrible that we dare not face it."

#### DIVERGENCE OF VIEWS THAT ARTISTS HOLD ON THE SAME SUBJECT

Bernard Shaw is justly considered as a notable man of letters. Anatole France is one of the greatest writers his country has produced. Mark Twain has a large following and yet the divergence of their views on as important a person as Jeanne D'Arc is impressive.

The Maid revolutionized Europe. A staunch Catholic, she instituted the belief, to the astonishment of the Church that she loved, that man was responsible to God alone for his actions. She wept when refused the privileges of the Church yet stoutly affirmed that her mission was from God.

Shaw who usually refuses to take anything seriously strangely regards Jeanne as sane and offers an ingenious but inadequate argument to prove his point. He insists that Jeanne's voices and visions were illusory because they

deserted her at a crucial moment, at a time when she needed their reassurance and comfort most, during her trial. When she was led to the stake and La Hire failed to batter down the gates of Rouen, when Warwick, who desired her speedy death, remained in power, she recanted. She donned woman's garb, which to her meant abject humiliation and the shattering of the bright vision that had led her on to victory, that had enabled her to crown the Dauphin king, at Rheims Cathedral. Shaw therefore assumes that this highly logical step was the product of a sane, orderly mind. He ignores the fact that insanity is a refuge for the mentally afflicted, that Jeanne created a visionary world because the every day one did not give her the gratification she derived from an imaginary sphere.

Her early youth was marked by stigmata upon which psychiatrists lay great stress. Seclusive, a dreamer, who watched her father's sheep, she peopled the green meadows of Domremy with angels who spoke to her. Saint Marguerite, Saint Catherine and Michael came down from the Heavens to talk with a child of twelve. They gave her advice and she would embrace them, intoxicated by their presence and fragrance. They were very intimate and oftentimes when it was dusk and she could not see them, they spoke to her from the bells. The quiet of the evening, the peace of the fields brought to her the voices of St Michael and Saint Catherine that she loved, that guided her to glory and the stake. Her heart that was impelled by heavenly guidance was cast into the river Seine. She was not of this earth, she was a

Saint, a genius, abnormal. Her recantation, due to imminent peril was transient. She reverted to her miraculous world because it was the only one in which her tortured mind could find peace. What though it led to the stake and a pitifully prolonged death? The flames that embraced her body and the waters of the Seine that received her heart were only physical agents. The power and intensity of her mind have survived to the amazement of a rather mechanical age.

Anatole France, scholar, artist, approached the truth more closely than did Shaw. Great enough to realize that keen observation and a skilled pen are not sufficient in themselves to thoroughly understand a person who requires medical attention, he sought the aid of Dr G. Dumas, a French psychiatrist, who reservedly made the diagnosis of Hysteria in Jeanne D'Arc. Anatole France approached Jeanne in an uncharitable spirit. He would not understand the Maid or her age. To properly appreciate his views of her one need only study his "Thais." He made of this courtesan a splendid creature indeed. Beautiful, admired, surrounded by luxury, sought by the gifted and distinguished, she led a riotous existence. Then seeing the first faint imprint of age, remembering a scene of her childhood in which a Christian slave took part, she sought refuge in that institution which welcomes the sinner. She ended as gloriously as she had lived. She tasted life to the full and died sanctified.

The spirit of Anatole France permeates the book. It is his Credo. He reverts to it time after time. It contains the commandment of "Thou

shalt not let joy pass thee by Life is gratification" Paphnuce, the lover of Thais, who leaves her to enter the desert, who lies on a hard rock and does penance, has a sorry end France despised him, and condemns him to an ignoble death He was incapable of understanding renunciation Abstinence was to him not only a negative but a hideous quality It was not life, it was the denial of life He thought that Paphnuce was a fool and Thais justified

He could understand Mary Magdalene but not Jeanne D'Arc She wore man's clothes, this incomprehensible creature, fought like a man, slept on the floor side by side with her comrades-in-arms, charged the English at the head of her soldiers, was wounded by an arrow which pierced her breast and died at the stake uttering the name of Jesus, seven times France was an ardent disciple of Voltaire and carried in his heart his Master's words, "Ecrasez l'infâme" France disliked the Church although he was capable of deep religious conviction as his "Christ de L'Océan" testifies, the religion of motives rather than that of formulae was his belief

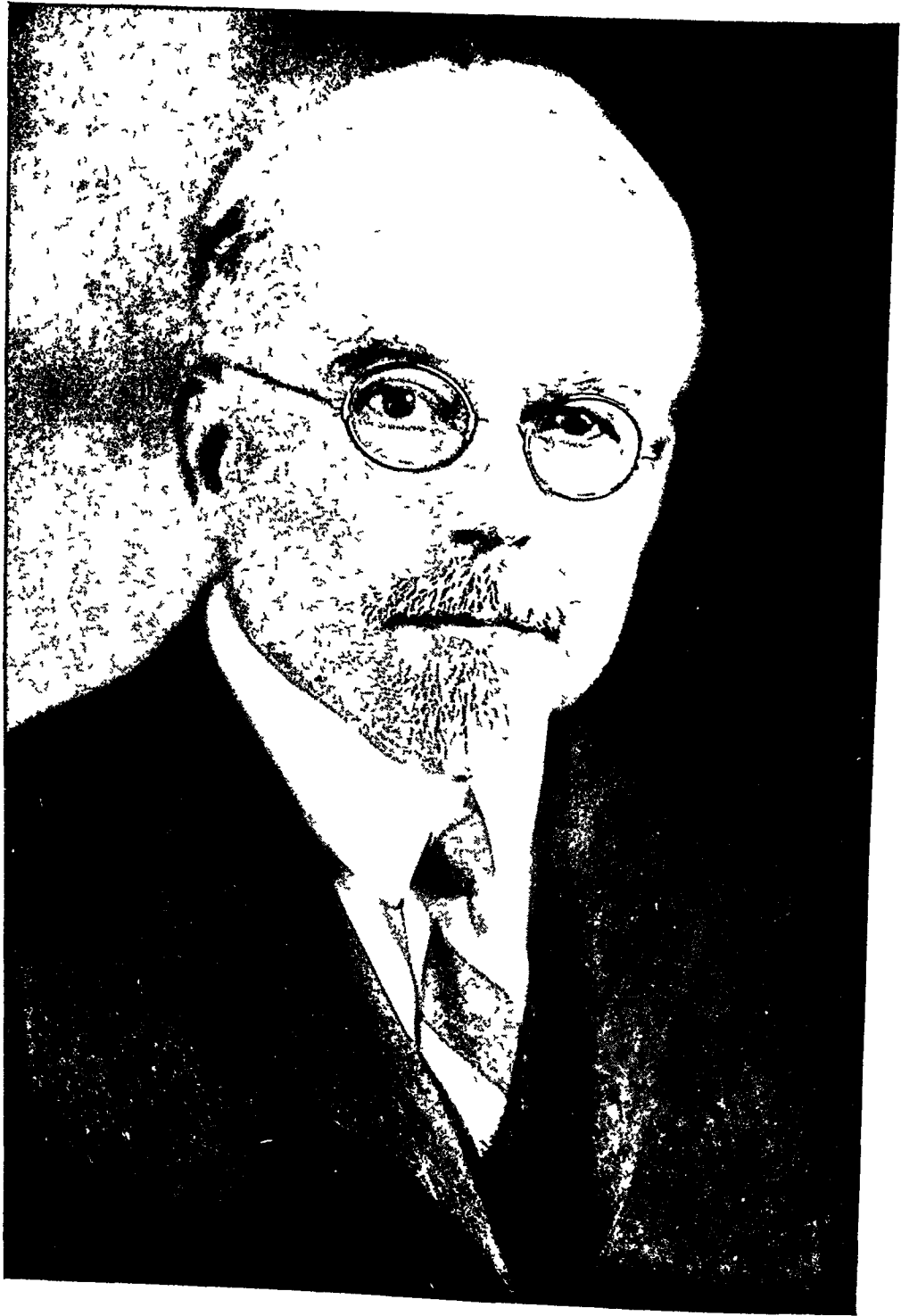
The world has been fortunate in possessing an accurate narration of the Maid's trial Despite this reliable evidence, two prominent authors, Shaw

and France, disagree utterly on crucial points, her sanity, her methods Shaw believed her sane, a good soldier and a statesman France asserted that she was insane, that Dunois was the brains behind it all and that clerical prompting was responsible for her religious zeal He denied that she had marked military and political ability

Mark Twain made a very ladylike creature of a domineering warlike maid, an incongruous picture He avoided the real Jeanne D'Arc He preferred that which Shaw terms a Victorian lady

The artist whether he judge Maid or physician often differs from his fellow craftsman on crucial points He sees through the veil of his early training, bias and mental make-up His views resemble those of many historians, they make delightful fiction The truth is often not in them Shaw will move mountains to gain a point France repudiated motives which he admired intensely because they lay in the heart of a religious girl, one so devout, that she died for the Church she loved, crying out the name of her God who died as she had The Maid will live despite her burning and the physician will still heal the ill, comfort the dying, despite all the Moheres, Flauberts, and Shaws of the world





Aldred Scott Warthin, 1866-1931

# Editorial

## Aldred Scott Warthin

Through the death of Aldred Scott Warthin the American College of Physicians has lost not only a Master, its First Vice-President, and the Editor of the *ANNALS* since 1924, but also a wise counselor and loyal friend. Once convinced of the intrinsic value of the College, he gave freely to it of his time and energy. With that foresight which characterized also his scientific investigations, he was able to visualize the important place which the College was to occupy and the extent to which it was to become a potent factor in fostering high standards of achievement in Internal Medicine and its related branches. This prophetic vision and this faith are most happily finding justification and realization, but Dr Warthin was far from being satisfied for he felt that, after all, the College was only entering upon its career of usefulness. In a letter to President S Marx White, dictated less than forty-eight hours before his death and left unsigned, Dr Warthin said, in part "I think that I would like to be on the program next year at the California meeting. So many men have written to me concerning various matters pertaining to the College that I would like to make an address bearing upon the future of the College and its functions \* \* \* \* The editorial which I had in the number preceding the meeting of the College apparently excited a

good deal of thought, and I am glad to see that there is a growing appreciation that the College should some time have something more than mere scientific work \* \* \* \* I think that there is a real opportunity to make the College a more vital force and influence in American Medicine than it is at the present time." Doctor Warthin must have had concrete suggestions in mind as he dictated these words. What they were, we can only surmise in part, but we can be sure that they were constructive and not destructive, for he would have planned the fullest possible utilization of existing agencies. The counsels which he had in mind, one can be sure, had had opportunity for crystallization during that period when time for reflective deliberation was provided by an enforced absence from the laboratory and its daily hurried routine, but they were not conceived in that interval. They were the outgrowth of a rich experience, forty years as a teacher, investigator and clinical pathologist. How rich this experience was, is revealed in the historical sketch which appears elsewhere in this number of the *ANNALS*. His major research activities alone show a breadth of interests which goes far to explain why Dr Warthin has exerted a significant influence, although usually an unconscious one, in the affairs of the Col-

lege The first four years of his teaching experience, under Doctor George Dock, were devoted to Internal Medicine It was during this period that the then young Demonstrator of Internal Medicine described in one of his early papers the accentuation of the pulmonary second sound in pericarditis and assigned diagnostic significance to it This alteration in the quality of the heart sounds has since been known as 'Warthin's sign' The same ability to make detailed objective scientific observations and to deduce from them conclusions, oftentimes at variance with prevailing views or far in advance of them, characterized his entire career as an investigator Moreover, while Dr Warthin believed fully in the value of pure science and in the worth of research for its own sake, he was always able to perceive the clinical application of new facts and to turn them to practical account In his description of the hemolymph nodes and demonstration of them as organs *sui generis* together with other studies upon the blood-forming system, he anticipated our present conception of the reticuloendothelial apparatus — only that cumbersome, yet convenient, name was lacking His early recognition of the importance of the thymico-lymphatic constitution, followed more recently by other studies upon pathological constitutional types as they are related to the etiology of neoplasms, pernicious anemia and Graves' disease, showed his appreciation of the importance of an aspect of the causation of disease which has not yet received the general acceptance which it deserves As early as 1904, and again in 1906, he vigorously recorded his belief in the

genetic unity of the group which includes the lymphosarcomas, chloroma, the leukemias and Hodgkin's disease, and he lived to see most workers in this field accept this generalization The first of the long series of papers on the pathology of syphilis appeared in 1910 Concerned originally with the lesions of congenital syphilis, Dr Warthin soon recognized the essential unity of the pathology of syphilis as found in various organs and in various stages of the disease Fortifying his position by the demonstration of the causal organism in lesions in which its presence had never before been proven—largely through original methods developed in his own laboratory—he founded a new conception of the pathology of latent syphilis and described the characteristic lesions as they occur in the heart, aorta, pancreas, adrenals and testes But in this, as in all his other work, it was the clinical application which was uppermost in his mind These few illustrations will serve to show the manner and degree in which all of Dr Warthin's investigative work aided in making him an important factor in American Medicine and in the College But to knowledge, to experience and to clinical judgment, there were added personality and character Unusually apt in public address, energetic and convincing in his manner of presentation, Dr Warthin's share in the programs of the College never failed to provoke thought Fearless, honest and above suspicion of ulterior motives, he was able to criticize without arousing animosity He imparted some of his own energy to every phase of the activities of the College with which he

was concerned. An attempt, then, on the part of anyone else to formulate those suggestions which Dr Warthin proposed to offer at the California meeting must be feeble, if not presumptuous. We can be sure that they would have been wise, practical, constructive, unselfish and inspiring. It is not unlikely that he would have urged consideration of ways and means for securing more general social and intellectual contact between the members of the College—something more than the contact of the “shop.” A greater emphasis, too, upon the cultural aspects of Medicine, and upon the value of those recreational activities, such as medical book-collecting, which are natural by-products of the thoughtful pursuit of Medicine, would

have been proposed. Certainly, too, he would have discussed the importance of casting the weight of influence of the College against the wholesale adoption of temporarily popular, but actually ephemeral, methods of diagnosis and treatment, for he felt strongly that too often, in the espousal of “fads,” physician and patient are alike deluded, and that here, if anywhere, there is a weak link in the chain of medical economics. Long and close association leads us to believe that we are right in these assumptions. How fortunate would the College have been, and how grateful and happy we all, if Aldred Scott Warthin had lived to give the College his message! Yet his influence will do much to guide its course for years to come.

## Abstracts

### *The Use of Cortin in Addison's Disease*

By FRANK A HARTMAN, A H AARON, and J E CULP (Endocrinology, 14 438-442 (Nov-Dec), 1930)

As previously shown by Hartman and his associates, cortin, a substance obtained from the adrenal cortex, enables adrenalectomized cats and rats to survive indefinitely. If Addison's disease is due to a deficiency of cortin the injection of this substance should ameliorate the disease. A patient, a man 24 years old, who was apparently moribund, has been kept alive for more than five months by this method. When first seen he was in shock with a pulse pressure of 50/20 mm. He was cold and drowsy, complained that his extremities felt numb, and talked irrationally. Twenty-four hours after admission, 5 cc of cortical extract was injected intravenously followed by further sub-cutaneous injections in 10 cc quantities until 150 cc had been given in 24 hours. Under this régime there was marked clinical improvement, particularly after the third day. The amount of cortin administered was gradually reduced until he was receiving only 20 cc in 24 hours. On the eleventh day there was a severe relapse, followed by symptomatic improvement when the dosage was again increased. Five months after treatment was instituted the patient was still much improved clinically. Four relapses had occurred, each following reduction of the dosage. A few hours after increasing the extract after each relapse, improvement was evident, and in two or three days recovery was almost complete. The appetite returned and mental activity became normal. It is difficult to account for these effects except through the action of cortin. Each relapse was accompanied by a fall in blood pressure and a rise in blood urea. Blood sugar was low during or after a relapse.

### *Experimental Production of Acute and Chronic Nephritis by the Injection of Bismuth Compounds* By PASTEUR VALLERY-RADOT, MAURICE DÉROT, and Mlle P GAUTHIER-VILLARS (Revue Belge des Sciences Médicales, 3 319-323, April, 1931)

By the intramuscular injection of an oily suspension of bismuth hydroxide the authors were able to produce in young rabbits evidences of acute, sub-acute, and chronic nephritis with azotemia, albuminuria, and tubular lesions in the kidneys. The suspension used contained the bismuth compound in an amount equivalent to 0.0646 grams of metallic bismuth per cubic centimeter. The doses employed in the production of nephritis were from 8 to 17 times greater than those used therapeutically in man. With the introduction of 0.50 cc daily, per kilo of rabbit, all the animals used showed an azotemia which was independent of malnutrition. Some showed a transient albuminuria. Death occurred in from 9 to 17 days. With daily injection of 0.20 cc of the suspension, the animals survived from 37 to 75 days. Chronic intoxication was accomplished by using smaller amounts or increasing the interval between successive doses. Histological changes were found to be in accord with those noted by others. Glomerular lesions were relatively slight, consisting of congestion in the earlier cases, intracapsular serous exudate and in four instances evidence of proliferation of the endocapsular lining. Tubular changes were to be found especially in the convoluted segments and varied from swelling of the tubular epithelium to complete necrosis and desquamation. Calcification in the renal tubules occurred in ten animals. In one, dying on the ninth day, it was so marked as to render the cutting of sections difficult. (Note by Editor: These and simi-

lar investigations of the effects of bismuth compounds upon the kidneys are of great importance. There can be no doubt that the relatively insoluble salts of bismuth, when administered over long periods of time, as is often the case in self-medication, may produce a chronic tubular nephritis. When this occurs the histological changes are essentially the same as described above.)

*On the Principles of Renal Function* By GOSTA EKEHORN (Acta Medica Scandinavica, Supplementum xxxvi, 1931)

This monograph of 717 pages presents the results of an investigation extending over a period of four years, the experimental portion of which was performed at the University of Oxford in the laboratory of Dr J G Priestley. By glomerulo-puncture, but with refinements in micro-physical and micro-chemical methods, which are minutely described, the glomerular urine of frogs was made available for volumetric titration and comparison with the blood and with the bladder urine of the same animal. The author concludes that at present it is impossible to formulate more than a fragmentary explanation of how the urine is normally formed, and still less is it possible to explain the pathological aberrations from the normal. As to the long-standing questions of filtration and resorption or renal secretion, however, he definitely favors the former to the exclusion of any form of selective secretion. The glomeruli filter and the resulting filtrate is produced in a volume which is from 100 to 200 fold that of the resulting bladder urine, the rate varying a good deal under different conditions. The tubules elaborate the filtrate into urine exclusively by reabsorbing into the blood the excess water and the excess amounts of all other urinary constituents contained in the large volume of filtrate, they resorb quantitatively from the filtrate all diffusible plasma constituents that fail to appear in the bladder urine. It is possible, although there is no definite evidence, that some of the metabolic products of the tubular epithelial cells may be added directly to the urine during this process. It is unlikely that the composite fluid reabsorbed by the tubules is of constant composition as held by Cushny, and

it is especially because of this that it is necessary to await further data in order to be able to construct a complete theory of normal and pathological renal behavior.

*The Relation of Monilia Psilosis to Tropical Sprue and an Evaluation of Fermentation of Sugar as a Criterion for Specificity* By BAILEY K ASHFORD (The Porto Rico Journal of Public Health and Tropical Medicine, 6 310-333, March, 1931)

Of 163 cases of clinical sprue, 127, or 77.9 per cent were positive for *Monilia psilosis*, 14, or 8.5 per cent, were positive for an atypical *Monilia psilosis*, another 14 were positive for a monilia similar to two strains which were converted by passage into *Monilia psilosis*. On the other hand, of 76 cases which were not sprue, *Monilia psilosis* was found in 14, or 18.4 per cent, but 13 of these were manifestly suffering from indigestion or diarrhea. Of 178 presumably healthy persons, only 5.6 per cent were found to be carriers. Sprue is generally insidious, and it complicates many slowly progressive fatal diseases of the tropics such as tuberculosis, cancer and dysentery. Malnutrition is usually the real basis for sprue, and upon it sprue is usually engrafted. In 50 per cent of such cases, not clinically sprue, a typical *Monilia psilosis*, or some nearly related or atypical form thereof, has been found in the feces. Some of these may be clinically unrecognizable cases of sprue. This does not prove that *Monilia psilosis* is the cause of sprue. Favorable conditions provided by a diseased digestive system may offer a medium for a harmless saprophyte. However, if this organism is a proven pathogen elsewhere, as in the tongue of thrush, the lung, tonsils, bone and skin, one should be guarded in stating that it is not related to sprue. The fermentation reactions, cultural characteristics and morphology of the organisms investigated in connection with the study of this large series of cases led to the suggestion that *Monilia albicans*, *Monilia psilosis*, *Monilia Pinosi*, and others may be one and the same yeast-budding fungus first described by Robin in 1853.

## Reviews

*Laboratory Medicine A Guide for Students and Practitioners* By DANIEL NICHOLSON, M D, Member of the Royal College of Physicians, London, Assistant Professor of Pathology, University of Manitoba, Assistant in Pathology, Winnipeg General Hospital 433 pages, 108 text figures and colored plate Lea and Febiger, Philadelphia, 1930 Price, \$6 00, net

In this book will be found detailed information on the indications, methods and interpretation of useful laboratory tests that a medical practitioner should be able to do. More highly technical diagnostic procedures which are apt to be performed in a large laboratory are also discussed as to the principles involved and proper interpretation. Preceding the technical section there are a number of charts and outlines indicating the choice of tests in various disease conditions. Some teachers of Internal Medicine will object to this card-index approach to the subject. The laboratory procedures proper are presented in fourteen chapters beginning with the methods of examination of the blood and ending with a description of essential laboratory equipment and lists of reagents. This book will prove to be of great value to the practitioner who performs the simpler tests himself, particularly those that can be done at the bedside, and will be useful to the laboratory technician. Technical methods for the preparation of microscopical sections of tissues are omitted except for the rapid method described by Terry. Since this guide is not intended for institutional laboratories, this omission is doubtless wise, for an adequate presentation would have added too much to the size of the book. Unfortunately, the ability to diagnose tissue sections is not as casual a matter as is indicated by the statement that study of illustrations in the best texts in pathology and surgery and review of permanent sections will qualify the surgeon to interpret microscopic pictures.

*Textbook of Human Embryology* By CLEVELAND SYLVESTER SIMKINS, Ph D., Associate Professor of Anatomy, University of Tennessee Medical School, Memphis, Tennessee With 263 illustrations, some in colors xiv+469 pages F A Davis Company, Philadelphia, 1931 Price, \$4 50, net

This textbook of embryology should prove to be of more than usual interest to medical students because it lives up to its title in that whenever possible the descriptions of developmental processes are specifically those which apply to man. Only when direct evidence is not available from human material are other mammals utilized and then specific information is given as to wherein probable differences occur. Likewise, there is a frequent correlation of morphology with the functional aspects of development which tends to bridge the gap between pure embryology and anatomy on the one side, and normal and pathological physiology on the other. The sections on aberrations and arrests of development, while very brief, have a similar value in respect to teratology. The illustrations are very well chosen from many sources and are excellently reproduced in keeping with the good press work of the entire book. The bibliography would have been made more useful by grouping the items in sections or by page references to the text. This book can be highly recommended to the student, and also to the medical practitioner who subjects himself to the, by no means arduous, discipline of occasionally reading a new text in each of the pre-clinical branches.

*Human Physiology* By F R WINTON, M D, Lecturer in the Department of Physiology and Biochemistry, University College, London, and L E BAYLISS, Ph D, Assistant in the Department of Physiology and Biochemistry, University College, London, with a chapter on The

*Physiology of the Sense Organs* by R J Lythgoe, M D, and a foreword by G Lovatt Evans, D Sc (Lond), F R C P, F R S xiv+583 pages 227 illustrations P Blakiston's Son and Co, Inc, Philadelphia, 1931 Price in cloth, \$4 50

This book has been kept somewhat shorter than the usual major textbook of general physiology by restricting its subject matter more closely to that applying to the human animal, by omitting much anatomy, histology and biochemistry usually found in such books, and by leaving out practically all historical data. It aims to include all the factual material expected of the student in medical examinations. Well written and well printed, it is a book which is sure to give satisfaction to the student group. Carefully selected references point the way for those who wish to go more deeply into special fields. The introduction of numerous short excursions into the field of pathological physiology, such as caisson disease (but why was the word capitalized?) and hyperthyroidism will enliven the book for the average medical student, and is in accord with the general tendency in medical education to introduce clinical material at an earlier period in the curriculum.

*The Vegetative Nervous System. An Investigation of the Most Recent Advances* The Proceedings of the Association for Research in Nervous and Mental Disease, December 27th and 28th, 1928. Editorial Board: Walter Timme, M D, Thomas K Davis, M D, Henry Alsop Riley, M D xi+832 pages, 185 illustrations, and 19 tables. The Williams and Wilkins Company, Baltimore, 1930. Price, \$10 00.

This is Volume IX in the series of research publications of the Association for Research in Nervous and Mental Disease. Under sections dealing with the Morphology, Physiology, Experimental Investigation, Clinical Investigation and Therapy of the vegetative nervous system, are grouped the contributions of forty-five investigators, selected because of special interest and training in their respective fields. Adequate review of the subject matter of so many papers cannot be attempted, but the entire group constitutes a very complete, almost encyclopedic, presentation of the most re-

cent knowledge in this field. Because of the breadth of treatment, this monograph will be extremely useful to those working in the preclinical subjects, such as anatomy and histology, physiology and pathology, as well as to the clinical investigator and practitioner.

*Treatment of Epilepsy* By FRITZ B TALBOT, M D, Clinical Professor of Pediatrics, Harvard University Medical School, Chief of Children's Medical Department, Massachusetts General Hospital xiv+308 pages. The Macmillan Company, New York, 1930. Price, \$4 00.

It is intended that this book, concerned primarily with treatment, will supplement the monograph on epilepsy by Lennox and Cobb. It is much more than a therapeutic guide, however, for the author establishes the foundation for his major thesis by brief, well-written chapters dealing with the history, incidence, etiology, pathology and symptomatology of the disease. While other forms of therapy and management are discussed in appropriate sections, the second half of the book is devoted almost exclusively to dietary treatment, and, in particular, to the ketogenic diet. A bibliography of 306 selected references and an unusually detailed index complete the book, which can be recommended without reservations to those physicians interested in the care and treatment of epileptics.

*Household Physics* By WALTER G WHITMAN, Head of Department of Physical Science, State Normal School, Salem, Massachusetts, Editor of General Science Quarterly viii+437 pages 329 illustrations. John Wiley and Sons, Inc, New York City, 1930. Price, \$2 50, net.

This addition to the Wiley Technical Series gives simple well-illustrated explanations of the physics of many forms of household apparatus and of their operation. Such relatively modern contrivances as the small home refrigerating plant are discussed. This should be a useful book in the nurses' training school library, and will answer not a few questions for the doctor himself. Thus fortified, he may even succeed in securing some respect for his erudition and scientific acumen from those of his own household.



# College News Notes

## NOMINATING COMMITTEE FOR 1932

In accordance with the provisions of the By-Laws, Article I, Section 3 The President "shall appoint within one month after induction to office a Nominating Committee of five, composed of two members of the Board of Regents, two members of the Board of Governors and one Fellow at large, whose duty it shall be to nominate candidates for the elective offices, Board of Regents and Board of Governors. The selection of nominees for the Board of Governors shall be made after due consideration of suggestions of members from the respective states, provinces or districts which will be represented by the nominees, if elected. The list of nominees for President-Elect and for the first, second and third Vice Presidents shall be submitted to all the Masters and Fellows of the College at least one month before the annual meeting, and the election of all nominees shall be by the members of the College at its annual business meeting. This does not preclude nominations made from the floor at the annual meeting itself," President S Marx White, of Minneapolis, appointed the following Committee

W Blair Stewart, Governor  
Edward L Tuohy, Governor  
Noble Wiley Jones, Regent  
John H Musser, Regent  
Alfred Stengel, Fellow at Large,  
Chairman

Dr Mills Sturtevant (Fellow), Clinical Professor of Medicine at New York University, delivered a course in "Gastro-Intestinal Symptoms as an Approach to Diagnosis" in connection with an eight weeks' postgraduate course in Gastro-enterology recently given at the Health Center Building, Paterson, N J, by the New Jersey Medical Society in co-operation with Rutgers University Extension Division

Dr George B Eusterman (Fellow), Rochester, Minn, spoke before a joint meeting of the North End Medical Society and the North Branch of the Philadelphia County Medical Society at Philadelphia, May 7, his title being "Achlorhydria, Its Significance in Clinical Medicine and Gastro-Enterology"

In the May, 1931, issue of THE AMERICAN JOURNAL OF THE MEDICAL SCIENCES, Dr John B Youmans (Fellow), Nashville, Tenn, is the author of an article entitled, "Changes in the Skin in Thyrotoxicosis With a brief study of the Absorption Time of Intradermally Injected Salt Solution in Patients with Thyrotoxicosis"

The sixtieth annual session of the California Medical Association was held at San Francisco, April 27-30, under the Presidency of Dr Lyell C Kinney (Fellow), San Diego

Dr Alexander T Cooper (Fellow), Denver, addressed the Medical Society of the City and County of Denver, April 7, on "Some Observations on the Results of Phrenico-Exeresis in Pulmonary Tuberculosis"

The following Fellows of the College participated on the program of the Illinois State Medical Society's recent and annual meeting as indicated

Dr Walter M Simpson (Fellow), Dayton

"Recent Developments in Tularemia"

Dr. LeRoy Sante (Fellow), St Louis

"Factors Concerned in Radiation Therapy of Malignant Disease"

Dr William W Duke (Fellow), Kansas City

"Allergy as Related to the General Practice of Medicine"

Dr Edwin C Ernst (Fellow), St Louis  
"Present Status of Penetrating X-Rays  
and Radium in Deep-Seated Cancer and  
other Diseases"

Dr Walter C Alvarez (Fellow), Roch-  
ester, Minn, spoke before the Iowa State  
Medical Society, May 13-15, on "The Art  
of Medicine"

Dr Alvarez also gave the twentieth and  
last of the series of lectures at the New  
York Academy of Medicine, April 17, on  
"Problems of Gastro-Enterology Today"

Doctors Clifford A Barborka (Fellow),  
and William C MacCarty (Fellow), both  
of Rochester, Minn, were guest speakers at  
the sixty-fifth annual session of the State  
Medical Association of Texas, May 5-7  
Their subjects were "Present Status of the  
Ketogenic Diet and Its Use" and "Classi-  
fication, Diagnosis and Prognosis of Neo-  
plasms," respectively

Dr James Marr Bisailon (Fellow), Port-  
land, Ore, addressed the Arizona State  
Medical Association on "End-Results Fol-  
lowing Intrapleural Pneumolysis"

The Los Angeles County Medical Associ-  
ation was addressed, April 16, by Dr John  
V Barrow (Fellow), Los Angeles, on "Sig-  
nificance of Teeth in Focal Infections"

Dr James H Hutton (Associate), Chi-  
cago, addressed the Kane County (Ill) Med-  
ical Society, April 15, on "Relationship of  
Endocrinology to Obstetrics and Gynecol-  
ogy"

Dr Robert C Moehlig (Fellow), Detroit,  
spoke before the St Clair County (Mich)  
Medical Society, recently on endocrinology

Dr Hugo A Freund (Fellow), Detroit,  
was one of the speakers at the meeting  
of the Saginaw County (Mich) Medical  
Society on March 17 He delivered an ad-  
dress on arthritis

Dr Samuel H Snider (Fellow), Kan-  
sas City, Mo, addressed the Nodaway Coun-

ty (Missouri) Medical Society, recently, on  
"Artificial Pneumothorax the Other Lung"

Dr Joseph C Doane (Fellow), Phila-  
delphia, spoke on "What the Public Thinks  
of the Present Day Practice of Medicine"  
at a meeting of the fifth councilor district  
of the Medical Society of New Jersey, At-  
lantic City, April 10

The annual meeting of the New Mexico  
Medical Society was held at Albuquerque,  
May 20-22, under the Presidency of Dr  
Meldrum K Wylder (Fellow), Albuquer-  
que

Dr William Gerry Morgan (Fellow),  
Washington, D C, addressed the one hun-  
dred and twenty-fifth annual meeting of the  
Medical Society of the State of New York,  
which was held in Syracuse, June 1-3

The following Fellows of the College con-  
ducted a course in Internal Medicine at St  
John's Hospital, Tulsa, which was attended  
by 135 physicians of northern Oklahoma

Dr John H Musser (Fellow), New Or-  
leans, La

Dr Charles A Elliott (Fellow), Chicago,  
Ill

Dr Porter P Vinson (Fellow), Roch-  
ester, Minn

"Applied Therapeutics" was the subject  
of an address delivered by Dr Arthur C  
Morgan (Fellow), Philadelphia, April 9,  
before the Cambria County (Pennsylvania)  
Medical Society and the Cambria-Somerset  
Counties Pharmaceutical Association

Dr John O Mamer (Fellow), Nash-  
ville, and Dr Ernest R Zemp (Fellow),  
Knoxville, were re-elected Treasurer and  
Speaker of the House of Delegates, re-  
spectively, at the annual meeting of the  
Tennessee Medical Association

Dr Zemp presented a paper on calcium  
therapy before the Green County (Tennes-  
see) Medical Society recently

Dr George R Minot (Fellow), Boston,  
delivered the annual Alpha Omega Alpha

lecture at the Vanderbilt University School of Medicine, recently, on treatment of anemia

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Dr William R Bathurst (Fellow), Little Rock, Ark, was recently re-elected Secretary of the Arkansas Medical Society

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The New Haven County (Connecticut) Medical Association was addressed by Dr John H Foster (Fellow), Waterbury, on upper respiratory tract infections

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Dr Allen H Bunce (Fellow), Atlanta, recently addressed the Ninth District (Ga) Medical Society on "Focal Infection—Is It a Practical Theory?"

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Dr Herman N Bundesen (Fellow), Chicago, coroner of Cook County since 1928, was appointed Health Commissioner of Chicago by the newly elected Mayor

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Dr Samuel A Overstreet (Fellow), Louisville, Ky, addressed the Floyd County (Indiana) Medical Society, April 10, on "X-Rays in Gastric and Intestinal Disorders"

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Dr Oval N Bryan (Fellow), Nashville, spoke before the Christian County (Kentucky) Medical Society, April 21, on undulant fever

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Dr Virgil E Simpson (Fellow), Louisville, addressed the Third District Medical Society at Bowling Green, Ky, April 15, on "Classification of the Nephritides"

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Dr Paul D White (Fellow), Boston, was one of the guest speakers who participated in a symposium on the treatment of cardiovascular disease during the meeting of the Maine Medical Association, which was held at Portland on June 25-27

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Dr William J Stapleton, Jr (Fellow), Detroit, recently presented an original etching by Alfred Hutt, artist, of Dr William H Welch, of Baltimore, to the Wayne County (Michigan) Medical Society. The etching is autographed by Dr Welch, as

well as being signed by the artist, and was made in connection with the celebration of Dr Welch's eightieth birthday during 1930.

Dr Stapleton presented the "Preliminary Report of the Committee on Medicolegal Problems of the American Medical Association" before the joint meeting of the Wayne County Medical Society and the Detroit Bar Association at Detroit on May 5

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Medical Clinics given at the Hahnemann Medical College of Philadelphia by the following Fellows of the College were published in the April Issue of the Hahnemannian Monthly

Dr G Harlan Wells, Philadelphia "Slow Pulse, Its Significance, Diagnosis and Treatment"

Dr Carl V Vischer, Philadelphia "Acute Bronchitis"

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Dr Ray M Balyeat (Fellow), Oklahoma City, addressed the Lancaster County (Nebraska) Medical Society, April 21, on hay-fever and asthma

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Doctors Thomas R Brown (Fellow), Baltimore, and Edgar A Hines (Fellow), Seneca, S C, were among guest speakers at the seventy-eighth annual session of the Medical Society of the State of North Carolina. Their subjects were "Various Forms of Colitis, Their Etiology, Diagnosis and Treatment" and "Brief Pediatric Reminiscences and Probable Trends," respectively

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Doctors Claiborne T Smith (Fellow) and William Bernard Kinlaw (Fellow), both of Rocky Mount, N C, received the Moore County Medical Society Medal for their paper on "The Clinical Consideration of an Anemia of Pregnancy and the Puerperium"

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Dr Clifford J Straehley (Fellow), Cincinnati, delivered an address on "Common Heart Disease" before the Adams County Medical Society at West Union, Ohio, on April 22

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Dr Kenneth M Lynch (Fellow), Charleston, S C, addressed the Anderson County

(S C) Medical Society, recently, on "Intestinal Amebiasis"

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Dr Lawrence Getz (Fellow), Panama, was elected Secretary of the Medical Association of the Isthmian Canal Zone, recently

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Announcement has been made by Surgeon General Hugh S Cumming of the appointment of Dr W S Leathers (Fellow), Nashville, to membership of the National Advisory Health Council of the U S Public Health Service

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Dr Kenneth M Lynch (Fellow), Charleston, S C, is the author of a new book on "Protozoan Parasitism of the Alimentary Tract" Dr Lynch is Professor of Pathology at the Medical College of the State of South Carolina, and President of the South Carolina State Medical Association

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At the 39th annual session of the Oklahoma State Medical Association held at Oklahoma City, May 11-13, 1931, the following members contributed to the Program

Dr John H Musser (Fellow), New Orleans,

"The Normal and Diseased Heart" and  
"The Acute Infectious Diseases"

Dr Ray M Balyeat (Fellow), Oklahoma City,

"Recent Advancement in Allergy"

Dr Henry H Turner (Associate), Oklahoma City,

"Neuro-endocrine Problems in Children"

Dr Carroll M Pounders (Fellow), Oklahoma City,

Chairman's Address of the Oklahoma Pediatric Society

Dr Louis Faugeres Bishop, Jr (Fellow), New York City,

"Cardiac Pain"

Dr Lea A Riely (Fellow), Oklahoma City

"Chronic Pancreatitis, A Clinical Study"

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The following Fellows of the College recently received promotions at the Hahnemann Medical College of Philadelphia

Dr G Harlan Wells to Professor and Head of the Department of Medicine,  
Dr E Roland Snader, Jr, to Clinical Professor of Medicine,

Dr Donald R Ferguson to Clinical Professor of Medicine,

Dr Carl V Vischer to Associate Professor of Medicine

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Dr Arthur A Shawkey (Fellow), Charleston, W Va, gave a paper and led a roundtable discussion on the management of the acute gastro-intestinal conditions of infancy and early childhood during the meeting of the Fayette County (W Va) Medical Society on May 12

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At the recent meeting of the American Association for the Study of Gout held in Kansas City, Dr A Morris Ginsberg (Fellow), Kansas City, delivered a paper on "Hyperthyroidism and Diabetes Mellitus"

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Dr C Ray Lounsberry (Fellow), San Diego, presented a paper before the Dermatological Section at the meeting of the California State Medical Association in San Francisco, April 27, on the subject "Colored Movie Demonstration of Dermatological Lesions"

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Dr Allen R Foss (Fellow), Missoula, Mont, spoke before the Mount Powell Tri-County Medical Society at Deer Lodge on Coronary Thrombosis

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Dr Harold W Gregg (Fellow), Butte, Mont, recently spoke before the Western Montana Medical Society on "Neurologic Aspects of Brain Injury," and before the Cascade County Medical Society on "Neurologic Aspects of Brain Injury, with especial reference to Compensation Features, and End Results of Treatment"

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Dr V C Rowland (Fellow), Cleveland addressed the American Gastro-Enterological Society on "The Dietetic Control of some forms of Hypertension and their Associated Dyspepsias," May 4 and the Ohio State Medical Association, May 13 on

### "Aluminum Hydroxide Treatment of Peptic Ulcer"

At the Commencement exercises of Gettysburg College, on June 8, the degree of Doctor of Science was conferred upon Dr Jesse L. Lenker (Fellow), Harrisburg, Pa

Dr Curran Pope (Associate), Louisville, Ky, was the guest of the Tennessee State Medical Association's meeting at Knoxville, April 14-16. Dr Pope discussed a number of the papers that were presented

Dr Hyman I. Goldstein (Associate), Camden, N. J., is the author of the following papers appearing in medical journals as indicated:

"Hereditary Epistaxis, with and without Hereditary (Familial) Multiple Hemorrhagic Telangiectasia" or "Ullman-Goldstein's Heredo-Familial Angiomatosis with Hemorrhages" in the April, 1931, issue of the Journal of the Medical Society of New Jersey,

"Hemorrhages in Rendu-Osler-Weber's Disease" in the April issue of the Medical Review of Reviews (New York),  
 "Maggots in the Treatment of Infections" in Annals of Surgery, April, 1931 (N. Y.),

"Hereditary Epistaxis (Osler's Disease)" in the December, 1930, issue of International Clinics, Volume IV (40th series)

Dr David A. Tucker, Jr., (Fellow) and Dr Cecil Striker (Associate), both of Cincinnati, Ohio, addressed the Cincinnati Academy of Medicine, April 20, on insulin

Dr John W. Torbett (Fellow), Marlin, Texas, was recently elected a Vice President of the State Medical Association of Texas

Dr Charles C. Bass (Fellow), New Orleans, was one of the speakers at the annual meeting of the Medical Library Association, which was held in the New Hutchinson Memorial, Tulane University of Louisiana School of Medicine, May 19-21.

Dr. James Birney Guthrie (Fellow), New Orleans, has been appointed Professor of the Principles and Practice of Medicine and Head of the Department of Internal Medicine of the New Medical Center of Louisiana State University, according to the announcement of Dr J. M. Smith, President, and Dr Arthur Vidrine, Dean

Dr Guthrie is a graduate of the Tulane University of Louisiana School of Medicine, Class of 1900. He spent his internship at the Charity Hospital, and has been actively serving that hospital ever since, having been Chief of Medical Service No. 4 for many years. During the yellow fever epidemic of 1905 at New Orleans, Dr Guthrie was Resident Physician in the Emergency Hospital operated jointly by the U. S. Public Health Service and New Orleans citizens. For many years, he has been connected with Tulane University in a teaching capacity. Since 1912, he has been Professor of Clinical Medicine, terminating this appointment by resignation in July, 1930. Other appointments held by him include Consultant in Medicine, Touro Infirmary and a Member of the Staff of the Hotel Dieu. He is a Colonel in the Medical Reserve Corps of the U. S. Army

The Southern California Medical Association held its eighty-fourth semi-annual meeting, April 10-11. Officers for the past year included:

Dr Frederick B. Clarke (Fellow), Long Beach—*President*

Dr William H. Barrow (Fellow), San Diego—*First Vice President*

Dr Carl R. Howson (Fellow), Los Angeles—*Secretary-Treasurer*

Dr Walter C. Alvarez (Fellow), Rochester, Minn., was an invited guest speaker, giving a paper on "The Diagnosis of Gastro-Intestinal Disease from the History," and an evening address on "Some of the Practical Things I Have Learned During my Five Years at the Mayo Clinic."

Dr Harold H. Smith (Fellow), Los Angeles, discussed a paper on "Renal Insufficiency in Hypothyroidism."

The Hancock County (Ohio) Medical Society offered its members a special pro-

gram at Findlay on April 30, with the following members of the College making up the program

- Dr A H Waterman (Fellow), Chicago,  
 Dr Frank Wright (Fellow), Professor of Clinical Chemistry, Northwestern University, Chicago—"The Colloids of the Blood in Relation to Clinical Medicine",  
 Dr F J LeBlanc (Associate), Elgin, Ill—"Clinical Aspects and Application of the Colloids in the Blood"

Dr S U Marietta (Fellow), Major, M C, U S Army, has been assigned Chief of the Medical Service, Walter Reed General Hospital, Washington, D C, effective June 1, 1931

The Medical Clinic of the University of Pennsylvania Hospital has introduced into the curriculum this year a series of weekly addresses to the senior class by invited speakers. These will be popularly known as "Saturday at Eleven". Among eminent members of the American College of Physicians who have been chosen to deliver an address in the series, are the following

- Dr Alfred Stengel (Master), Philadelphia, Professor of Medicine, University of Pennsylvania,  
 Dr Warfield T Longcope (Fellow), Baltimore, Professor of Medicine, Johns Hopkins University,  
 Dr H R M Landis (Fellow), Philadelphia, Professor of Clinical Medicine, University of Pennsylvania,  
 Dr Walter W Palmer (Fellow), New York, Professor of Medicine, Columbia University,  
 Dr Maurice C Pincoffs (Fellow), Baltimore, Professor of Medicine, University of Maryland,  
 Dr Elmer H Funk (Fellow), Philadelphia, Clinical Professor of Medicine and Therapeutics, Jefferson Medical College,  
 Dr J C Meakins (Fellow), Montreal, Professor of Medicine, McGill University,  
 Dr William B Porter (Fellow), Richmond, Professor of Medicine, Medical College of Virginia,

- Dr Thomas B Fitcher (Fellow), Baltimore, Associate Professor of Clinical Medicine, Johns Hopkins University,  
 Dr Josephus T Ullom (Fellow), Philadelphia

At the monthly meeting of the Medical Society of Bay Ridge, Brooklyn, May 12, Dr Henry Monroe Moses (Fellow), Attending Physician to the King's County Hospital, Brooklyn, delivered a paper (by invitation) on "Carcinoma of the Lung"

Dr Joseph G Terrence (Fellow), Brooklyn, by invitation, discussed the above paper

The American Climatological and Clinical Association held its forty-eighth annual meeting at Hot Springs, Va, May 7-9, 1931, under the Presidency of Dr George Morris Piersol (Fellow), Philadelphia

Members of the Council of the American Climatological and Clinical Association who are Fellows of the American College of Physicians include

- Dr Roger I Lee, Boston  
 Dr Stuart Pritchard, Battle Creek  
 Dr Joseph Pratt, Boston  
 Dr Walter A Baetjer, Baltimore  
 Dr Gerald B Webb, Colorado Springs

The following Fellows contributed papers to the Program

- Dr William S McCann (Fellow), Rochester, N Y—"Conditions Associated with Pulmonary Arteriosclerosis",  
 Dr Thomas Klein (Fellow), Philadelphia—"The Treatment of Pericarditis with Effusion by Artificial Pneumopericardium",  
 Dr O H Perry Pepper (Fellow), Philadelphia—"Malignant Hypertension Simulating Cerebral Lesions",  
 Dr A H W Caulfield (Fellow), Toronto—"Non Post-operative Pulmonary Atelectasis",  
 Dr Charles Hartwell Cocke (Fellow), Asheville—"Pleural Shock",  
 Dr Lawrason Brown (Fellow), Saranac Lake—"A Study of 500 Cases of Pulmonary Tuberculosis with no or indefinite Physical Signs",  
 Dr Ralph C Matson (Fellow), Portland, Ore. (with Dr Ray W Matson)

—"The Electro-Surgical Method of Severing Adhesions in Artificial Pneumothorax",

Dr Kennon H Dunham (Fellow), Cincinnati—"A Study of Lung Anatomy as Seen in an X-Ray Plate which Demonstrates the Association of Emphysema with Chronic Pulmonary Tuberculosis",

Dr Thomas P Sprunt (Fellow), Baltimore—"Chronic Lymph Node Enlargement with Mononucleosis",

Dr Charles C Browning (Fellow), Los Angeles—"Report of Pathological Fracture of Two Ribs in a Case of Pulmonary Tuberculosis followed by extensive Emphysema of Cellular Tissue, Subcutaneous and Intra-muscular"

New Officers elected for 1931-32 include the following

President—Dr Louis Hamman (Fellow), Baltimore,

First Vice President—Dr Paul H Ringer (Fellow), Asheville,

Second Vice President—Dr William B Porter (Fellow), Richmond

New Council members include Dr Stuart Pritchard (Fellow), Battle Creek, and Dr George Morris Piersol (Fellow), Philadelphia

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At the thirty-fourth session of the American Gastro-Enterological Association, held at Atlantic City, May 4-5, 1931, the follow-

ing Fellows of the American College of Physicians were elected Officers of the Association

President—Dr. Clement R Jones (Fellow), Pittsburgh

Secretary—Dr Charles G Lucas (Fellow), Louisville

Treasurer—Dr Thomas Wray Grayson (Fellow), Pittsburgh

Recorder—Dr Sara M Jordan (Fellow), Boston

Members of the Council

Dr Walter C Alvarez (Fellow), Rochester

Dr Frank Smithies (Master), Chicago  
Committee on Admission and Ethics

Dr Harlow Brooks (Fellow), New York

Dr A H Aaron (Fellow), Buffalo

Dr B B Vincent Lyon (Fellow), Philadelphia

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On May 7, twenty-six vitamin experts from all parts of the country met at the Hotel Pennsylvania, New York, to discuss the standards for vitamin content and particularly those pertaining to cod liver oil and other vitamin containing preparations of the U S Pharmacopeia Dr Walter A Bastedo (Fellow), New York, President of the U S Pharmacopeial Convention, with Mr E Fullerton Cook, Chairman of the Pharmacopeia Revision Committee, represented the Pharmacopeia at the Conference.

## OBITUARIES

## DR ALDRED SCOTT WARTHIN

Aldred Scott Warthin, Professor of Pathology and Director of the Pathological Laboratories at the University of Michigan, died suddenly, on Saturday, May 23rd, at Ann Arbor. In Doctor Warthin's passing, American medicine lost an outstanding representative, pathology and the associated sciences, a great craftsman and teacher, the world, a scholarly and inspiring influence. But few persons have been granted a life so rich in usefulness and accomplishment as was Doctor Warthin's, and few, indeed, of our time, have had an educational foundation so adequate as to permit an outlook as broad-visioned as was his.

Doctor Warthin was born at Greensburg, Indiana, October 21st, 1866, the son of Edward Mason Warthin and Eliza Margaret (Weist) Warthin. His artistic bent and his recognized ability early turned him to music, and in 1887, he received a Teacher's Diploma in Music at the Cincinnati Conservatory. Thus was secured that opportunity for relaxation at the piano which served so well in years of stress. But music was not the end in view, as his life work. Doctor Warthin entered Indiana University and obtained the A. B. Degree in 1888. He then matriculated at the University of Michigan where he earned his A. M. in 1890, M. D. in 1891 and the Ph. D. in 1893. His career as teacher and investigator began at Michigan in 1891 and was continued in that school for nearly forty years.

Doctor Warthin's pathway to pathology followed that of several of the

then noted European scientists, namely, via the Department of Internal Medicine. Doubtless, while a post-graduate student at Vienna and Freiburg, this course was impressed upon him by that eminent pathologist Ziegler. So, from 1891 to 1895, inclusive, we find Doctor Warthin serving at Michigan, first, as Assistant in Internal Medicine and later, as Demonstrator. This clinical contact left an indelible impression upon him when, in 1896, he became Demonstrator in Pathology. To thousands of inspired students he taught pathology, not as an irksome chore with dead-house tissue but as an opportunity to study abnormalities responsible for the like ailments of patients they were observing in the Hospital wards. This early-acquired knowledge of internal medicine exerted a significant influence upon many of Warthin's later original researches and it raised his clinico-pathologic conferences to one of the outstanding didactic events in American pathology.

After his entrance into the Division of Pathology, Doctor Warthin's advancement was rapid. In 1897, Instructor, 1899, Assistant Professor, 1902, Junior Professor, and 1903, Professor and Director of the Pathological Laboratories. For the past twenty-eight years, he has thus served. During that period, the scientific contributions made by himself and his co-workers have brought his department to a position of international importance. Well does the writer recall the enthusiasm of noted foreign visitors as they observed Doctor Warthin's organization, his methods of teaching.



his autopsy classes and his beautiful museum specimens it seems but yesterday that Ehrlich exclaimed. "To think that I should have to come to America to see my triacid stain perfectly made!"

Doctor Warthin was interested not alone in creating a model department of Pathology in a great university, in both state and nation, his interests were many and always constructive. His capacity for work, talent for organization, and gift of logical and brilliant presentation were early recognized. He served as Secretary (1907-1918) of The Michigan Association for the Prevention and Relief of Tuberculosis and as President (1918-1919), President of the Michigan Social Hygiene Association (1917-1918), Secretary and President of The Ann Arbor Anti-Tuberculosis Association (1917-1918) and in a multitude of lesser capacities, too numerous to record. Nationally, he was honored by membership (and usually by being called to office) in the leading organizations of specialists in Medicine. He became President (1908) of the American Association of Pathologists and Bacteriologists; President (1924) of the American Society for Experimental Pathology, Delegate to the National Research Council (1925-1928), President of the American Association for Cancer Research (1928), President of the Association of American Physicians (1928), Master and First Vice-President of the American College of Physicians (from 1925), and President of the International Society of Medical History (1930-1931). He was a staunch supporter of organized medicine and exhibited it by his many

years of Fellowship in the American Medical Association and his interest in his state and local societies.

Internationally, Doctor Warthin was honored by the Presidency of the International Association of Medical Museums (1910-1913) and served as Editor of its Bulletin (1913-1919). He was a member of the Council for the United States (1914-1927), and Vice-President of the American Section from 1914. For many years he was Corresponding Member of the International Association for the Study and Prevention of Tuberculosis.

Doctor Warthin's capacity for sustained effort and the broad scope of his knowledge are attested by his numerous public addresses and by his writings. As a speaker, he was in constant demand throughout the country. His addresses were always masterly and stimulative. No American pathologist brought his subject before the general profession with greater clarity and impressiveness than did he.

Dealing chiefly with pathology and generally with his own investigations and those of his associates, his writings form an imposing bibliography. Particularly important are his *Practical Pathology* (1896, 1911); his editing and translating of the tenth and eleventh editions of *Ziegler's General Pathology* (1903, 1908); his timely, comprehensive war-time work (with Weller), *Medical Aspects of Mustard Gas Poisoning* (1919); his sections in *Pathology* in the second and third editions of Wood's *Reference Handbook of the Medical Sciences*. In 1929 appeared his remarkable, philosophic and widely-read book on *Old Age*, to be followed in 1930, by that mellowed,

comforting and inspiring *The Creed of a Biologist*. Both of these works received wide reading and were commented upon in gratifying and understanding fashion by the scientific and lay press. His last book appeared shortly before his death—it was the publication of an elaboration of his illustrated address (1930) before The American Association of the History of Medicine. Dr Warthin's interpretation of the Physician in that fantastic series of sketches, symbols and paintings, known universally as *The Dance of Death* was a fitting climax to a long series of scholarly writings.

Doctor Warthin's major researches are too well known to require repetition—he left his mark upon nearly all phases of pathology. As landmarks in the science of pathology are those studies dealing with the anatomy and pathology of hemolymph glands, the pathology of the blood and the blood-forming organs, cardiac syphilis, latent syphilis, tuberculosis and that remarkable investigation of the toxic action of mustard gas.

In June 27, 1900, the then Assistant Professor of Pathology married Katherine Angell of Chicago and to them four children were born: Margaret; Aldred Scott, the second, Virginia and Thomas Angell.

Elsewhere in this number of the Annals, the value of Doctor Warthin's association with The American College of Physicians will be considered, yet the writer feels that here, if only as a personal appreciation, a few lines should appear.

In 1923, weary, puzzled and discouraged by the task of creating as something worthwhile, an organization whose time of inception had been pre-

mature and whose course erratic, your correspondent went to Professor Warthin—as pupil to his teacher. He proved most cordial, receptive, and after hours of frank discussion, encouraging. After a few weeks' consideration, a letter came from Doctor Warthin, containing his application for Fellowship, his pledge of loyal support and a wise and vigorous discussion upon the College as it was and the College as it must become. From that day, Doctor Warthin never wavered in his support of what our organization was endeavoring to build. His attendance at committee meetings, his trips in the interest of College affairs, his addresses at annual sessions, his acceptance of the Editorship of the Annals (1924) and his splendid development of its pages, his broad vision and his characteristic, unswerving loyalty to his friends and the cause to which he was committed, had much to do with bringing the College to the distinguished position which it now occupies in American Medicine. So quietly and unselfishly were his efforts exerted that few Fellows realized what a potent influence he was in our advancement and in the very maintenance of the integrity of the College.

Our personal debt is beyond recognition.

Surely, so full, inspiring and productive a life and so worthy a comrade in our enterprise, suggests a form of recognition by the College, more substantial, lasting and appropriate than is supplied by this bare outline of Doctor Warthin's scientific career and achievements.

(Furnished by Frank Smithies, M D  
Sc D, M A C P, Chicago)

## DOCTOR GEORGE MARTIN KOBBER

Dr George Martin Kober (Fellow), Washington, D C , died, April 24, 1931, of heart disease; aged, 81 years

Dr Kober was born at Alsfeld, Hesse Darmstadt, Germany, March 28, 1850 He was educated at the grand ducal Realschule of his native town In 1867, he emigrated to the United States and secured an assignment to the Hospital Corps at Carlisle Barracks, Pa. He commenced his medical studies under Dr J J B Wright, U S A , and in January of 1870, was appointed Hospital Steward, and ordered to Frankford Arsenal, near Philadelphia There he continued his medical studies until October, 1871, when he was ordered to duty in the office of the Surgeon General of the Army at Washington He studied medicine under Doctors Johnson Eliot and Robert Reyburn, supra, and was the first graduate of a postgraduate course instituted by Doctors Thompson, Busey, Ashford and others at the Columbia Hospital for Women, in 1873 In 1874 he assisted in the reorganization of the Central Dispensary, and in providing a German-speaking staff for the benefit of his suffering countrymen In July, 1874, he was appointed Acting Assistant Surgeon, U S A ; then Post Surgeon at Alcatraz Island, Calif , then Post Surgeon, Fort McDermit, to July, 1877 He was in the field expedition, in southeastern Nevada, against the Indians in the Fall of 1875, and in the Nez Perces expedition and in charge of the field hospital at Kammah, on the Clearwater, Idaho, from July to October, 1877. He then became Post Surgeon at Camp near Spo-

kane Falls and Fort Couer d'Alene, to November, 1879, Fort Klamath, Oregon, to June, 1880, and at Fort Bidwell, Calif , to November, 1886 While at Fort Bidwell, he was engaged extensively in practice among civilians until June, 1887, when he travelled extensively in this country and Europe, returning to Fort Bidwell in 1888 Later in the same year, he returned to Washington, and in 1889 was appointed Professor of State Medicine, Georgetown University Medical School In August, 1890, he was appointed a member of the Tenth International Medical Congress and Honorary Secretary of one of its sections In December, 1890, he returned to Fort Bidwell, Calif In 1894, he established his permanent residence in Washington

Dr Kober was a Fellow of the American Association for the Advancement of Science, a member of the Association of American Physicians, a Fellow of the American Medical Association, an honorary member of the Association of Military Surgeons, a member and Ex-President of the Medical and Surgical Society of the District of Columbia, a member and Ex-President of the Medical Association of the District of Columbia, a member of the Washington Academy of Sciences, a member and Ex-President of the Washington Anthropological Society, an Ex-President of the Association of American Medical Colleges, and had been a Fellow of the American College of Physicians since March 10, 1923

Dr Kober was the author of the standard medical curriculum He was the one who in 1890 directed attention

to the pollution of the Potomac water as a factor in the undue prevalence of typhoid fever in Washington, and in 1895, at the request of the Health Officer and the District Commissioners, he investigated more fully the causes of typhoid fever in Washington, and was the first to point out the agency of flies in carrying the germs. His report was published in 1895. His public addresses on the relations of water supply and sewers to the health of the city, as well as his researches into the relative merits of slow-sand and mechanical filtration, helped to secure the necessary sanitary legislation and necessary appropriation by Congress.

He was one of the principal promoters of the Washington Sanitary Improvement Company, which offered to capital a safe five per cent investment, and at the same time secured to wage earners, and others of moderate resources, sanitary homes at reasonable rentals.

Dr Kober had been, at one time or another, a member of the Consulting Staffs of nearly every hospital in Washington. In May, 1907, he was appointed a member of the President's Homes Commission. As Chairman of the Committee on Social Betterment, he prepared a monograph on Industrial Hygiene and Social Betterment, published in 1908 as Senate Document No 644. This, with his monograph on Milk in Relation to Public Health, published in 1902 as Senate Document No 44, and his work on Urinology and its practical applications, constitute his most important writings. However, he was author of numerous other articles and co-author of books on "Industrial Health" and "Diseases of Occupation-

al and Vocational Hygiene." Few have been honored so highly or have had so long an active career.

(Furnished by William Gerry Morgan, M D, F A C P, Governor for the District of Columbia.)

### COLONEL BELL BURR, A M , M D

The recent death of Doctor Colonel Bell Burr removes an unique, interesting and much beloved character from the medical life of Michigan. Dr Burr died April 11, 1931, at the age of 74.

For many years he had been the efficient head of the Oak Grove Sanitarium for Nervous and Mental Diseases at Flint. Prior to that he was Medical Superintendent of the Eastern Michigan Hospital at Pontiac. He was a man of wide mental range, a member of many learned societies, an author of valuable books and numerous contributions to periodical medical literature, a man of great versatility, a delightful personality, and an outstanding figure in the medical profession of Michigan.

Dr Burr was born in Lansing, Michigan, November 3, 1856. His early education was obtained in public schools of his native city. He attended the Medical Department of the University of Michigan and graduated from the College of Physicians and Surgeons of New York in 1878.

Dr Burr will be well remembered as a great neurologist and as a useful and leading member of many important professional societies. He was President of the Michigan State Medical Society and served long and efficiently on its council. He was a Fel-

low of the American College of Physicians and of the American Medical Association; a member of the American Neurological Association, Secretary and later President of the American Psychiatric Society and member of the Société Medico-Psychologique of Paris, France. He served faithfully on the Michigan State Board of Registration in Medicine, was President of the Detroit Society of Neurology and Psychiatry and Fellow of the Detroit Academy of Medicine. Near the close of his career the University of Michigan conferred upon Dr Burr the Honorary Degree of Master of Arts as a tribute to his achievements.

Dr Burr was a writer of clearness, force, and dependable value. His work on "Practical Psychology and Psychiatry" is a most useful contribution to medical science. His most important work, for which he will be long and gratefully remembered, is his two-volume "Medical History of Michigan."

As a man and a friend he is gratefully remembered. His tender and sympathetic nature sweetened his manly character and held those who knew him best in genuine fellowship. He possessed an analytic mind which faced the problems of social and public life with the same penetration as that by

which he solved the problems of his chosen science, and he devoted himself to every allotted task with the unflagging energy with which he carved his career to professional eminence and public affection. He will be held in high esteem not only for his professional work but for his great charm of character, his fine ideals, his devotion to righteousness and truth, his unselfishness, integrity, friendliness, and love of his fellowmen.

(Furnished by Charles D Aaron, M.D., F.A.C.P., Detroit, Mich.)

### DOCTOR LOUIS MICHAEL GOMPERTZ

Dr. Louis Michael Gompertz (Associate), New Haven, Conn., died, February 22, 1931, of coronary occlusion; aged, 58 years.

Dr. Gompertz received the degree of Doctor of Medicine from Yale University School of Medicine, 1896. For several years, he had been the Assistant Clinical Professor of Gastro-enterology at Yale University School of Medicine, Attending Gastro-enterologist to the Hospital of St. Raphael, Attending Physician to the New Haven County Home and Consulting Gastro-enterologist to the Grace Hospital.





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